



Europäisches Patentamt
European Patent Office
Office européen des brevets



Publication number:

0 395 446 A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 90304648.0

(51) Int. Cl.⁵: C07D 295/18, C07D 333/24,
C07D 213/56, A61K 31/495,
A61K 31/44, A61K 31/38

(22) Date of filing: 27.04.90

(30) Priority: 28.04.89 JP 111295/89

(43) Date of publication of application:
31.10.90 Bulletin 90/44

(94) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(98) Date of deferred publication of the search report:
29.05.91 Bulletin 91/22

(71) Applicant: Sankyo Company Limited
5-1 Nihonbashi Honcho 3-chome Chuo-ku
Tokyo(JP)

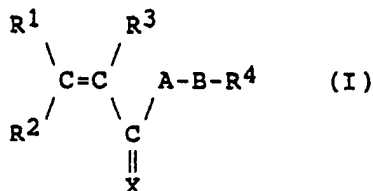
(72) Inventor: Nakamura, Norio, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Ohkawa, Nobuyuki, c/o Sankyo

Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Oshima, Takeshi, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Miyamoto, Masaaki, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Tjijima, Yasuteru, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)

(74) Representative: Gibson, Christian John Robert
et al
MARKS & CLERK 57/60 Lincoln's Inn Fields
London WC2A 3LS(GB)

(54) N-acryloylpiperazine derivatives, their preparation and their use as paf antagonists.

(57) Compounds of formula (I):



pharmaceutically acceptable salts thereof have valuable PAF antagonist activity, and may be prepared by reacting a compound containing the piperazine or homopiperazine part of the molecule with a compound containing the other part of the molecule.

EP 0 395 446 A3

[in which R¹ and R² is each -R⁵, -CH=CH-R⁵ or -C=C-R⁵, in which R⁵ is optionally substituted aryl or aromatic heterocyclic; R³ is hydrogen, alkyl, cyano or -R⁵; X is oxygen or sulphur; A is 1,4-piperazin-1,4-diyl or a 1,4-homopiperazin-1,4-diyl; B is alkylene, carbonyl, thiocarbonyl, sulphonyl or sulphonyl; and R⁴ is optionally substituted phenyl] and



Eur p an
Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 30 4648

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 083 712 (HOKURIKU PHARMACEUTICAL CO.) * Page 1, lines 1-19 * - - -	1	C 07 D 295/18 C 07 D 333/24
A	FR-A-2 209 560 (DEUTSCHE GOLD- UND SILBER-SCHEIDE-ANSTALT) * Page 1, line 1 - page 2, line 15 * - - -	1	C 07 D 213/56 A 61 K 31/495 A 61 K 31/44
A	FR-A-1 388 838 (FARBWERKE HOECHST AG) * Page 1, line 1 - page 2, line 5; examples * - - -	1	A 61 K 31/38 C 07 D 295/22
A	EP-A-0 120 321 (CELAMERCK GmbH) * Pages 1-3 * - - - - -	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 295/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search The Hague		Date of completion of search 27 February 91	Examiner PAUWELS G.R.A.
<div>CATEGORY OF CITED DOCUMENTS</div> <div>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention</div> <div>E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons &: member of the same patent family, corresponding document</div>			



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

**0 395 446
A2**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 90304648.0

(51) Int. Cl.⁵: C07D 295/18, C07D 333/24,
C07D 213/56, A61K 31/495,
A61K 31/44, A61K 31/38

(22) Date of filing: 27.04.90

(30) Priority: 28.04.89 JP 111295/89

(43) Date of publication of application:
31.10.90 Bulletin 90/44

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(71) Applicant: Sankyo Company Limited
5-1 Nihonbashi Honcho 3-chome Chuo-ku
Tokyo(JP)

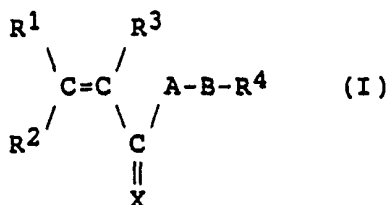
(72) Inventor: Nakamura, Norio, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Ohkawa, Nobuyuki, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi

Shinagawa-ku, Tokyo 140(JP)
Inventor: Oshima, Takeshi, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Miyamoto, Masaaki, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)
Inventor: Tjijima, Yasuteru, c/o Sankyo
Company Limited
No. 2-58, 1-chome Hiromachi
Shinagawa-ku, Tokyo 140(JP)

(74) Representative: Gibson, Christian John Robert
et al
MARKS & CLERK 57/60 Lincoln's Inn Fields
London WC2A 3LS(GB)

(54) N-acryloylpiperazine derivatives, their preparation and their use as paf antagonists.

(57) Compounds of formula (I):



[in which R¹ and R² is each -R⁵, -CH=CH-R⁵ or -C=C-R⁵, in which R⁵ is optionally substituted aryl or aromatic heterocyclic; R³ is hydrogen, alkyl, cyano or -R⁵; X is oxygen or sulphur; A is 1,4-piperazin-1,4-diyl or a 1,4-homopiperazin-1,4-diyl; B is alkylene, carbonyl, thiocarbonyl, sulphonyl or sulphonyl; and R⁴ is optionally substituted phenyl] and pharmaceutically acceptable salts thereof have valuable PAF antagonist activity, and may be prepared by reacting a compound containing the piperazine or homopiperazine part of the molecule with a compound containing the other part of the molecule.

EP 0 395 446 A2

N-ACRYLOYLPIPERAZINE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS PAF ANTAGONISTS

The present invention relates to a series of novel N-acryloylpiperazine derivatives which have PAF antagonist activity and provides processes for preparing these derivatives, as well as methods and compositions using them for the treatment of various diseases and disorders arising from imbalances in the PAF system in the mammalian, e.g. human, body.

5 The abbreviation "PAF" is used herein with its conventional meaning of "platelet activating factor".

Natural PAF, at least as isolated from mammalian tissues, is a mixture of from 2 to 5 phospholipids, the number depending upon the nature of the original tissue. The formulae of the major constituents of PAF are now well known. Natural PAF is laevorotatory and the various components of natural PAF may be identified, for example as: 1-C_{16:0} = PAF where the alkoxy group at the PAF 1-position is a hexadecyloxy group; 1-C_{18:0} = PAF where the alkoxy group at the PAF 1-position is an octadecyloxy group; or 1-C_{18:1} = PAF where the alkoxy group at the PAF 1-position is a 9-(Z)-octadecenyloxy group. The convention used above for identifying the constituents of PAF gives the rotation first (1, in the above examples), followed by the number of carbon atoms in the 1-alkoxy group, and finally the number of double bonds.

PAF exhibits a strong platelet activating and aggregating effect, from which it derives its name. It has, however, in recent years been seen to be a potentially crucial mediator in a wide variety of pathological processes. Thus, it also has a hypotensive effect and increases vasopermeability; it is believed to be an active agent in the induction of the shock state (for example endotoxin-induced shock or anaphylactic shock) and to act as a mediator of inflammatory disease. It has also been found to play an important role in nephritis, myocardial infarction, angina pectoris, asthma, cardiac and systemic anaphylaxis, gastric and intestinal ulceration, psoriasis and immune and renal disorders. In addition, it is believed that PAF antagonists may be useful for prophylaxis of rejection in organ transplantation.

It is not, therefore, surprising that, as a result, PAF antagonists have been investigated with a view to developing new types of treatment for the above pathologies, and notably new types of anti-shock agent and anti-inflammatory agent. Accordingly, various compounds have been investigated in an attempt to find such PAF antagonists, and, currently, several compounds are known as PAF antagonists. Although the chemical structure of known PAF antagonists varies widely, and there appears to be no obvious common factor linking all of their chemical structures, in general, known materials having PAF-antagonist activity may be classified according to their chemical structure as either PAF type or non-PAF type compounds. The compounds of the present invention are non-PAF type compounds, and specifically are compounds containing an N-acryloylpiperazine or N-acryloylhomopiperazine system.

Amongst known such compounds which have structures similar to those of the compounds of present invention and which are said to have similar types of activities are:

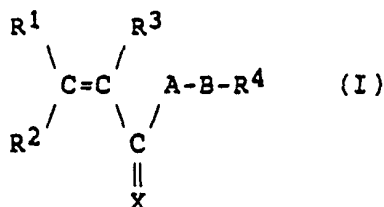
the pentadienylamido compounds disclosed, inter alia, in US Patent No. 4 788 206;
the alkenyl-, alkenoyl- or thioalkenoyl- amido compounds disclosed, inter alia, in European Patent Publication No. 298 466; and
the polycycloalkylcarbonyl- piperazine or homopiperazine compounds disclosed, inter alia, in European Patent Publication No. 284 359.

Also known are the N-nicotinoylpiperazine derivatives of Japanese Patent Application Kokai No. Sho. 60-193966, which are structurally related to the compounds of the present invention, but these are only disclosed to have peripheral vasodilating and anti-hypertensive activities, and there is no suggestion that these compounds may have PAF antagonist activity.

The compounds of the prior art referred to above all have structures different from those of the compounds of the present invention, although, in some cases, the prior compounds may share elements of the structures of the compounds of the present invention. In particular, none of the prior compounds is an N-acryloylpiperazine or N-acryloylhomopiperazine compound.

We have now discovered a series of new N-acryloylpiperazine and N-acryloylhomopiperazine derivatives which have excellent PAF antagonist activity and many of which have shown an excellent and wholly unexpected stability, even when administered orally, to give a high blood concentration of the active compound. The activities of many of the compounds of the present invention have shown indications of being substantially better than those of the compounds of the prior art, including those referred to above and having structures similar to those of the compounds of the present invention.

In accordance with the present invention, there are provided, as new compounds, those acryloylpiperazine and acryloylhomopiperazine compounds having the formula (I):



10 in which:

R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,

in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a), defined below, or an aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (a), defined below;

R³ represents a hydrogen atom, a C₁ - C₆ alkyl group, a cyano group, or a group having the formula -R⁵, in which R⁵ is as defined above;

X represents an oxygen atom or a sulphur atom;

A represents a 1,4-piperazin-1,4-diyl group or a 1,4-homopiperazin-1,4-diyl group;

B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group, a sulphinyl group or a sulphonyl group;

R⁴ represents an unsubstituted phenyl group or a substituted phenyl group which is substituted by from 1 to 5 of substituents (a) and/or substituents (b), defined below;

substituents (a):

C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; hydroxy groups; C₁ - C₄ alkylenedioxy groups; C₁ - C₂₂ aliphatic carboxylic acyloxy groups; substituted C₁ - C₆ aliphatic carboxylic acyloxy groups which are substituted by at least one of substituents (c), defined below; C₇ - C₁₅ carbocyclic aromatic carboxylic acyloxy groups; substituted C₇ - C₁₅ carbocyclic aromatic carboxylic acyloxy groups which are substituted by at least one of substituents (d), defined below; C₈ - C₁₅ aralkyloxycarbonyloxy groups in which the aryl part is unsubstituted or is substituted by at least one of substituents (d), defined below; C₁ - C₆ alkanesulphonyloxy groups in which the alkane part is unsubstituted or is substituted by at least one of substituents (c), defined below; arylsulphonyloxy groups in which the aryl part is unsubstituted or is substituted by at least one of substituents (d), defined below; halogen atoms; and nitro groups;

substituents (b):

C₁ - C₆ alkylsulphonyl groups; C₁ - C₆ alkylsulphinyl groups; and C₁ - C₆ alkylthio groups;

substituents (c):

C₁ - C₆ alkyl groups; C₁ - C₆ haloalkyl groups; halogen atoms; C₁ - C₆ alkoxy groups; and (C₁ - C₆ alkanoyloxy)methoxycarbonyl groups;

substituents (d):

C₁ - C₆ alkyl groups; C₁ - C₆ alkoxy groups; halogen atoms; unsubstituted C₆ - C₁₀ aryl groups; nitro groups; and (C₁ - C₆ alkoxy)carbonyl groups; and pharmaceutically acceptable salts thereof.

The invention also provides a pharmaceutical composition for the treatment or prophylaxis of PAF-related diseases and disorders, comprising at least one PAF antagonist in combination with a pharmaceutically acceptable carrier or diluent, in which the PAF antagonist is at least one compound of formula (I), as defined above, or a pharmaceutically acceptable salt thereof.

The invention still further provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in medicine.

The invention still further provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the treatment or prophylaxis of a PAF-mediated pathology, such as psoriasis, nephritis, asthma, inflammation or shock.

The invention still further provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of medicament for the treatment or prophylaxis of a PAF-mediated pathology, such as psoriasis, nephritis, asthma, inflammation or shock.

The invention also provides processes for the preparation of the compounds of the present invention, which are described in greater detail hereafter.

In the compounds of the present invention R¹ and R² are the same or different and each represents a

group of formula $-R^5$, $-\text{CH}=\text{CH}-R^5$ or $-\text{C}\equiv\text{C}-R^5$, where R^5 is as defined above.

Where R^5 represents an aryl group, this is a carbocyclic aryl group which has from 6 to 14, preferably from 6 to 12 and more preferably from 6 to 10, ring carbon atoms, and which may be substituted or unsubstituted. Where the group is substituted, the substituents are selected from substituents (a), defined above and exemplified below. Examples of such unsubstituted groups include the phenyl and naphthyl (1-or 2-naphthyl) groups, preferably the phenyl group.

It is believed that the nature of the substituents on the phenyl or other aryl groups represented by R^5 , which may be, or may be included in, the groups represented by R^1 and R^2 , may have a significant effect on the efficacy of the compounds of the present invention, although the exact nature of this effect has not been fully elucidated. In general, we prefer those compounds where R^1 and/or R^2 represents a group R^5 , and more prefer those where R^1 and/or R^2 represents a group R^5 where R^5 represents an aryl group; most preferably one of the groups represented by R^5 is a substituted phenyl group and the other is an unsubstituted phenyl group or a substituted phenyl group. Still more preferably, in the group R^5 represented by, or included in the group represented by, R^1 , there is an electron-donating substituent (e.g. a methoxy group) or an electron-withdrawing substituent (e.g. a chlorine atom) on the aryl group; and, in the group R^5 represented by, or included in the group represented by, R^2 , there is no substituent, an alkyl substituent or an electron-withdrawing substituent on the aryl group. This applies even when R^1 and/or R^2 represents a group of formula $-\text{CH}=\text{CH}-R^5$ or $-\text{C}\equiv\text{C}-R^5$, but these compounds are most preferred when R^1 and R^2 are different and both represent a group of formula $-R^5$.

Where R^2 represents a substituted phenyl group, it is preferably substituted at least at the meta-position.

Examples of groups and atoms which may be included within substituents (a) are:

$C_1 - C_{22}$ alkyl groups, which may be straight or branched chain groups, such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, 2-methylbutyl, neopentyl, hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, t-pentyl, isohexyl, 1-methylpentyl, heptyl, 1-methylhexyl, 2-methylhexyl, 5-methylhexyl, 3-ethylpentyl, octyl, 2-methylheptyl, 5-methylheptyl, 2-ethylhexyl, 2-ethyl-3-methylpentyl, 3-ethyl-2-methylpentyl, nonyl, 2-methyloctyl, 7-methyloctyl, 4-ethylheptyl, 3-ethyl-2-methylhexyl, 2-ethyl-1-methylhexyl, decyl, 2-methylnonyl, 8-methylnonyl, 5-ethyloctyl, 3-ethyl-2-methylheptyl, 3,3-diethylhexyl, undecyl, 2-methyldecyl, 9-methyldecyl, 4-ethylnonyl, 3,5-dimethylnonyl, 3-propyloctyl, 5-ethyl-4-methyloctyl, dodecyl, 1-methylundecyl, 10-methylundecyl, 3-ethyldecyl, 5-propylnonyl, 3,5-diethyloctyl, tridecyl, 11-methyldodecyl, 7-ethylundecyl, 4-propyldecyl, 5-ethyl-3-methyldecyl, 3-pentyloctyl, tetradecyl, 12-methyltridecyl, 8-ethyldodecyl, 6-propylundecyl, 4-butyldecyl, 2-pentylnonyl, pentadecyl, 13-methyltetradecyl, 10-ethyltridecyl, 7-propyldodecyl, 5-ethyl-3-methyldodecyl, 4-pentyldecyl, hexadecyl, 14-methylpentadecyl, 6-ethyltetradecyl, 4-propyltridecyl, 2-butyldodecyl, heptadecyl, 15-methylhexadecyl, 7-ethylpentadecyl, 3-propyltetradecyl, 5-pentyldodecyl, octadecyl, 16-methylheptadecyl, 5-propylpentadecyl, nonadecyl, 17-methyloctadecyl, 4-ethylheptadecyl, icosyl, 18-methylnonadecyl, 3-ethyloctadecyl, henicosyl and docosyl groups, preferably a straight or branched chain alkyl group having from 1 to 6 carbon atoms, and more preferably a straight or branched chain alkyl group having from 1 to 4 carbon atoms;

$C_1 - C_{22}$ alkoxy groups, which may be straight or branched chain groups, such as the methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentoxy, isopentoxy, 2-methylbutoxy, neopentoxy, hexyloxy, 4-methylpentoxy, 3-methylpentoxy, 2-methylpentoxy, 3,3-dimethylbutoxy, 2,2-dimethylbutoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy, 2,3-dimethylbutoxy, t-pentoxy, isohexyloxy, 1-methylpentoxy, heptyloxy, 1-methylhexyloxy, 2-methylhexyloxy, 5-methylhexyloxy, 3-ethylpentoxy, octyloxy, 2-methylheptyloxy, 5-methylheptyloxy, 2-ethylhexyloxy, 2-ethyl-3-methylpentoxy, 3-ethyl-2-methylpentoxy, nonyloxy, 2-methyloctyloxy, 7-methyloctyloxy, 4-ethylheptyloxy, 3-ethyl-2-methylhexyloxy, 2-ethyl-1-methylhexyloxy, decyloxy, 2-methylnonyloxy, 8-methylnonyloxy, 5-ethyloctyloxy, 3-ethyl-2-methylheptyloxy, 3,3-diethylhexyloxy, undecyloxy, 2-methyldecyloxy, 9-methyldecyloxy, 4-ethylnonyloxy, 3,5-dimethylnonyloxy, 3-propyloctyloxy, 5-ethyl-4-methyloctyloxy, dodecyloxy, 1-methylundecyloxy, 10-methylundecyloxy, 3-ethyldecyloxy, 5-propylnonyloxy, 3,5-diethyloctyloxy, tridecyloxy, 11-methyldodecyloxy, 7-ethylundecyloxy, 4-propyldodecyloxy, 5-ethyl-3-methyldodecyloxy, 3-pentyloctyloxy, tetradecyloxy, 12-methyltridecyloxy, 8-ethyldodecyloxy, 6-propylundecyloxy, 4-butyldodecyloxy, 2-pentylnonyloxy, pentadecyloxy, 13-methyltetradecyloxy, 10-ethyltridecyloxy, 7-propyldodecyloxy, 5-ethyl-3-methyldodecyloxy, 4-pentyldodecyloxy, hexadecyloxy, 14-methylpentadecyloxy, 6-ethyltetradecyloxy, 4-propyltridecyloxy, 2-butyldodecyloxy, heptadecyloxy, 15-methylhexadecyloxy, 7-ethylpentadecyloxy, 3-propyltetradecyloxy, 5-pentyldodecyloxy, octadecyloxy, 16-methylheptadecyloxy, 5-propylpentadecyloxy, nonadecyloxy, 17-methyloctadecyloxy, 4-ethylheptadecyloxy, icosyloxy, 18-methylnonadecyloxy, 3-ethyloctadecyloxy, henicosyl and docosyl groups, preferably a straight or branched chain alkoxy group having from

1 to 6 carbon atoms, and more preferably a straight or branched chain alkoxy group having from 1 to 4 carbon atoms;

C₁ - C₆ haloalkyl groups, in which the alkyl part may be any one of those alkyl groups exemplified above, and is more preferably a C₁ - C₄ alkyl group, and the halogen atom may be a fluorine, chlorine, bromine or iodine atom, preferably a fluorine or chlorine atom, such as the fluoromethyl, trifluoromethyl, difluoromethyl, 5 dichloromethyl, dibromomethyl, trichloromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, 2-haloethyl (e.g. 2-chloroethyl, 2-fluoroethyl, 2-bromoethyl or 2-iodoethyl), 2,2-dibromoethyl, 2,2,2-tribromoethyl, pentafluoroethyl, 4-chlorobutyl, 4-bromobutyl and 4-fluorobutyl groups, preferably the trifluoromethyl, trichloromethyl and pentafluoroethyl groups;

10 hydroxy groups;

C₁ - C₄ alkylenedioxy groups in which the alkylene part may be a straight or branched chain group; examples include the methylenedioxy, dimethylenedioxy, trimethylenedioxy, tetramethylenedioxy, ethylenedioxy and isopropylidenedioxy groups, of which the methylenedioxy group is preferred;

15 carbon-carbon double or triple bonds or may be free from such bonds, and in the case of the unsaturated groups, the number of carbon atoms is preferably from 3 to 6 (and, in any case, has to be at least 3); examples of such groups include the alkanoyloxy groups, such as the formyloxy, acetoxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy, isovaleryloxy, octanoyloxy, nonylcarbonyloxy, decylcarbonyloxy, 3-methylnonylcarbonyloxy, 8-methylnonylcarbonyloxy, 3-ethyloctylcarbonyloxy, 3,7-dimethyloctylcarbonyloxy, 20 undecylcarbonyloxy, dodecylcarbonyloxy, tridecylcarbonyloxy, tetradecylcarbonyloxy, pentadecylcarbonyloxy, hexadecylcarbonyloxy, 1-methylpentadecylcarbonyloxy, 14-methylpentadecylcarbonyloxy, 13,13-dimethyltetradecylcarbonyloxy, heptadecylcarbonyloxy, 15-methylhexadecylcarbonyloxy, octadecylcarbonyloxy, 1-methylheptadecylcarbonyloxy, nonadecylcarbonyloxy, icosylcarbonyloxy and henicoylcarbonyloxy groups; unsaturated analogues of these alkanoyloxy groups, especially the C₃ - C₆ alkenoyloxy and alkynoyloxy groups, such as the (E)-2-methyl-2-butenoyloxy group; alkoxy carbonyloxy 25 groups, especially C₂ - C₇ alkoxy carbonyloxy groups (i.e. the alkoxy part is C₁ - C₆), such as the methoxycarbonyloxy, ethoxycarbonyloxy, t-butoxycarbonyloxy and isobutoxycarbonyloxy groups; such alkoxy carbonyloxy groups having one or more halogen or trialkylsilyl substituents in which each alkyl group, which may be the same or different, has from 1 to 4 carbon atoms, and in which one such alkyl group may 30 be replaced by a phenyl group), such as the 2,2,2-trichloroethoxycarbonyloxy and 2-trimethylsilylethoxycarbonyloxy groups; and the alkenyloxy carbonyloxy groups, such as the vinyloxy carbonyloxy and allyloxy carbonyloxy groups;

substituted C₁ - C₆ aliphatic carboxylic acyloxy groups which are substituted by at least one of substituents (c), defined above and exemplified more generally below; the acyloxy part may be any of the C₁ - C₆ (c), defined above and exemplified more generally below; the acyloxy part may be any of the C₁ - C₆ 35 unsubstituted acyloxy groups exemplified above, and specific examples of the substituted groups include: the halogenated alkanoyloxy groups, such as the chloroacetoxy, dichloroacetoxy, trichloroacetoxy and trifluoroacetoxy groups; the alkoxyalkanoyloxy groups, such as the methoxyacetoxy group; and the (C₁ - C₆ alkanoyloxy)methoxycarbonyl groups, such as the pivaloyloxymethoxycarbonyloxy group;

C₇ - C₁₅ preferably C₇ - C₁₁, carbocyclic aromatic carboxylic acyloxy groups (i.e. an arylcarbonyl group in 40 which the aryl part is C₆ - C₁₄, preferably C₆ - C₁₀), which may be unsubstituted or may have one or more substituents selected from substituents (d), defined above and exemplified more generally below; examples of such unsubstituted groups include the benzoyloxy, α -naphthoyloxy and β -naphthoyloxy groups; the substituted groups may be any of these unsubstituted groups but having at least one, and preferably from 1 to 5, more preferably from 1 to 3, of substituents (d); examples of the substituted groups include: 45 halogenated arylcarbonyloxy groups, such as the 2-bromobenzoyloxy and 4-chlorobenzoyloxy groups; arylcarbonyloxy groups substituted by one or more lower (i.e. C₁ - C₆, preferably C₁ - C₄) alkyl groups, such as the 2,4,6-trimethylbenzoyloxy and p-toluoyloxy groups; arylcarbonyloxy groups substituted by one or more lower (i.e. C₁ - C₆, preferably C₁ - C₄) alkoxy groups, such as the 4-anisoyloxy group; arylcarbonyloxy groups substituted by one or more nitro groups, such as the 4-nitrobenzoyloxy and 2-nitrobenzoyloxy groups; arylcarbonyloxy groups substituted by one or more lower (i.e. C₂ - C₇, preferably 50 C₂ - C₅) alkoxy carbonyl groups, such as the 2-(methoxycarbonyl)benzoyloxy group; and arylcarbonyloxy groups substituted by one or more aryl groups, such as the 4-phenylbenzoyloxy group;

C₈ - C₁₅ aralkyloxy carbonyloxy groups in which the aryl part is C₆ - C₁₀ and the alkyl part is correspondingly C₁ - C₄; these groups may be unsubstituted or may have at least one substituent, 55 preferably on the aryl part or parts, selected from substituents (d), defined above and exemplified more generally below, preferably one or two lower alkoxy or nitro groups; the alkyl part is preferably unsubstituted; examples of such unsubstituted groups include the benzyloxy carbonyloxy group; and examples of such substituted groups include the unsubstituted groups referred to but substituted by one or more,

preferably from 1 to 5, more preferably from 1 to 3, of substituents (d), such as the 4-methoxybenzyloxycarbonyloxy, 3,4-dimethoxybenzyloxycarbonyloxy, 2-nitrobenzyloxycarbonyloxy and 4-nitrobenzyloxycarbonyloxy groups;

- 5 C₁ - C₆ alkanesulphonyloxy groups in which the alkane part is unsubstituted or is substituted by at least one of substituents (c), defined above and exemplified more generally below, preferably halogen atoms and more preferably fluorine atoms; examples of such groups include the lower (i.e. C₁ - C₆, preferably C₁ - C₄) alkanesulphonyloxy groups, such as the methanesulphonyloxy, ethanesulphonyloxy and 1-propanesulphonyloxy groups; and fluorinated lower alkanesulphonyloxy groups, such as the trifluoromethanesulphonyloxy and pentafluoroethanesulphonyloxy groups;
- 10 arylsulphonyloxy groups in which the aryl part is C₆ - C₁₀ and may be unsubstituted or may be substituted by at least one of substituents (d), defined above and exemplified more generally below; examples of such unsubstituted groups include the benzenesulphonyloxy group, and examples of such substituted groups include the unsubstituted groups referred to but substituted by one or more, preferably from 1 to 5, more preferably from 1 to 3, of substituents (d), such as the *p*-toluenesulphonyloxy group;
- 15 halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms, preferably the fluorine, chlorine and bromine atoms; and nitro groups.

Where substituent (a) is one of the aforementioned acyloxy groups, it may, if desired, be an acyloxy group which is easily hydrolysed *in vivo*, so as to form a pro-drug, which may be administered as the ester [substituent (a) is the acyloxy group], and is then converted to the free acid [substituent (a) is a hydroxy group], *in vivo*. Examples of such groups include: the (C₁ - C₆ alkanoyloxy)methoxycarbonyloxy groups, especially the pivaloyloxymethoxycarbonyloxy group; the alkanesulphonyloxy groups, especially the methanesulphonyloxy, ethanesulphonyloxy and 1-propanesulphonyloxy groups; the fluorinated alkanesulphonyloxy groups, especially the trifluoromethanesulphonyloxy and pentafluoroethanesulphonyloxy groups;

25 and the arylsulphonyloxy groups, especially the benzenesulphonyloxy and *p*-toluenesulphonyloxy groups.

Examples of groups and atoms included in substituents (c) are:

- the C₁ - C₆, preferably C₁ - C₄, alkyl groups, such as those exemplified above in relation to substituents (a); the C₁ - C₆, preferably C₁ - C₄, haloalkyl groups, such as those exemplified above in relation to substituents (a), and especially the trifluoromethyl and pentafluoroethyl groups;
- 30 halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms, especially the chlorine and fluorine atoms;
- the C₁ - C₆, preferably C₁ - C₄, alkoxy groups, such as those exemplified above in relation to substituents (a), and especially the methoxy group; and
- the (C₁ - C₆ alkanoyloxy)methoxycarbonyl groups, such as the formyloxymethoxycarbonyl, acetoxy-methoxycarbonyl, propionyloxymethoxycarbonyl, butyryloxymethoxycarbonyl, isobutyryloxymethoxycarbonyl, pivaloyloxymethoxycarbonyl, valeryloxymethoxycarbonyl and isovaleryloxymethoxycarbonyl groups, especially the pivaloyloxymethoxycarbonyloxy group.
- 35

Examples of groups and atoms included in substituents (d) are:

- the C₁ - C₆, preferably C₁ - C₄, alkyl groups, such as those exemplified above in relation to substituents (a);
- 40 the C₁ - C₆, preferably C₁ - C₄, alkoxy groups, such as those exemplified above in relation to substituents (a), and especially the methoxy group;
- halogen atoms, such as the fluorine, chlorine, bromine and iodine atoms, especially the chlorine and fluorine atoms;
- C₆ - C₁₀ aryl groups which are not substituted, such as the phenyl or naphthyl groups;
- 45 the nitro group; and
- C₂ - C₇ alkoxy-carbonyl groups (i.e. the alkoxy part is C₁ - C₆), such as the methoxycarbonyl, ethoxycarbonyl, *t*-butoxycarbonyl and isobutoxycarbonyl groups.

Examples of aromatic heterocyclic groups which may be represented by R⁵ include aromatic 5- to 14-membered heterocyclic groups, which may be monocyclic or condensed ring polycyclic groups, and whose ring atoms include from 1 to 5, preferably from 1 to 3, sulphur and/or oxygen and/or nitrogen atoms. Such groups have at least one ring having aromatic character, and, where there are two or more rings, these preferably, but not necessarily, all have aromatic character. Where the group is a condensed ring system, at least one of the rings must be a heterocyclic ring, and the other or others may be heterocyclic or non-heterocyclic, e. g. a benzene ring. Examples of such groups include the furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, isothiazolyl, thiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, carbolinyl, phenanthridinyl and acridinyl groups. Of these, we prefer the aromatic 5- to 10-membered heterocyclic groups, which

55

may optionally be condensed, having 1 or 2 sulphur and/or oxygen and/or nitrogen atoms, and more preferably the furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, quinolyl and isoquinolyl groups.

We most prefer that R^1 should represent a substituted phenyl group which is substituted by at least one of the aforementioned alkyl, alkoxy or halogen substituents and that R^2 should represent an unsubstituted phenyl group or a substituted phenyl group which is substituted by at least one of the aforementioned alkyl, haloalkyl and halogen substituents.

Examples of the $C_1 - C_6$ alkyl groups which may be represented by R^3 include those groups referred to above in relation to the alkyl groups which may be included within substituents (a), of which the straight and branched chain alkyl groups having 1 to 4 carbon atoms are preferred.

R^3 may also represent any of the groups defined and exemplified above for R^5 , or it may represent a cyano group or a hydrogen atom, but it is preferably a hydrogen atom.

X may represent an oxygen or sulphur atom, but is preferably an oxygen atom.

Where B represents an alkylene group, this has from 1 to 6 carbon atoms, and examples include the methylene, methylmethylene, ethylene, propylene, trimethylene, tetramethylene, 1-methyltrimethylene, 2-methyltrimethylene, 3-methyltrimethylene, pentamethylene and hexamethylene groups, of which the methylene, ethylene, trimethylene and tetramethylene groups are preferred.

B may also represent a carbonyl group, a thiocarbonyl ($>C=S$) group, a sulphonyl ($>SO_2$) group or a sulphinyl ($>SO$) group. Most preferably B represents a carbonyl group.

R^4 represents a phenyl group which may be unsubstituted or may have at least one substituent selected from substituents (a) and (b). Substituents (a) are both defined and exemplified above. Substituents (b) are defined above, and examples include:

lower alkylsulphonyl groups, which may have from 1 to 6, preferably from 1 to 4, carbon atoms in the alkyl part thereof, which itself may be a straight or branched chain group such as those exemplified in relation to the alkyl groups which may be included in substituents (a); examples of preferred such alkanesulphonyl groups include the methanesulphonyl, ethanesulphonyl, propanesulphonyl, isopropanesulphonyl, butanesulphonyl, isobutanesulphonyl, sec-butanesulphonyl, t-butanesulphonyl, pentanesulphonyl, isopentanesulphonyl, 2-methylbutanesulphonyl, neopentanesulphonyl, hexanesulphonyl, 4-methylpentanesulphonyl, 3-methylpentanesulphonyl, 2-methylpentanesulphonyl, 3,3-dimethylbutanesulphonyl, 2,2-dimethylbutanesulphonyl, 1,1-dimethylbutanesulphonyl, 1,2-dimethylbutanesulphonyl, 1,3-dimethylbutanesulphonyl and 2,3-dimethylbutanesulphonyl groups, of which the straight and branched chain alkanesulphonyl groups having from 1 to 4 carbon atoms are preferred;

lower alkylsulphinyl groups, which may have from 1 to 6, preferably from 1 to 4, carbon atoms in the alkyl part thereof, which itself may be a straight or branched chain group such as those exemplified in relation to the alkyl groups which may be included in substituents (a); examples of preferred such alkanesulphinyl groups include the methanesulphinyl, ethanesulphinyl, propanesulphinyl, isopropanesulphinyl, butanesulphinyl, isobutanesulphinyl, sec-butanesulphinyl, t-butanesulphinyl, pentanesulphinyl, isopentanesulphinyl, 2-methylbutanesulphinyl, neopentanesulphinyl, hexanesulphinyl, 4-methylpentanesulphinyl, 3-methylpentanesulphinyl, 2-methylpentanesulphinyl, 3,3-dimethylbutanesulphinyl, 2,2-dimethylbutanesulphinyl, 1,1-dimethylbutanesulphinyl, 1,2-dimethylbutanesulphinyl, 1,3-dimethylbutanesulphinyl and 2,3-dimethylbutanesulphinyl groups, of which the straight and branched chain alkanesulphinyl groups having from 1 to 4 carbon atoms are preferred; and lower alkylthio groups, which may have from 1 to 6, preferably from 1 to 4, carbon atoms in the alkyl part thereof, which itself may be straight or branched chain group such as those exemplified in relation to the alkyl group which may be included in substituents (a); examples of preferred such alkylthio groups include the methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, 2-methylbutylthio, neopentylthio, hexylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 3,3-dimethylbutylthio, 2,2-dimethylbutylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio and 2,3-dimethylbutylthio groups, of which the straight and branched chain alkylthio groups having from 1 to 4 carbon atoms are preferred.

We most prefer those compounds of the present invention in which R^4 represents a phenyl group having at least one $C_1 - C_3$ alkoxy, and more preferably methoxy, substituent, and most preferred are those compounds where R^4 represents a 3,4-dimethoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl or 3,4,5-trimethoxyphenyl group.

Certain of the compounds of the present invention can form salts. There is no particular restriction on the nature of these salts, provided that, where they are intended for therapeutic use, they are pharmaceutically acceptable. Where they are intended for non-therapeutic uses, e.g. as intermediates in the preparation of other, and possibly more active, compounds, even this restriction does not apply. The compounds may include at least one basic nitrogen atom, where B represents a $C_1 - C_6$ alkylene group, and can, therefore, form acid addition salts. Examples of such acid addition salts include: salts with a mineral acid, especially a

hydrogen halide (such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid), nitric acid, perchloric acid, sulphuric acid or phosphoric acid; salts with an organic carboxylic acid, such as fumaric acid, succinic acid, citric acid, tartaric acid, oxalic acid, maleic acid or malic acid; salts with a sulphonic acid, especially a lower alkanesulphonic acid (such as methanesulphonic acid, trifluoromethanesulphonic acid or ethanesulphonic acid) or an arylsulphonic acid (such as benzenesulphonic acid or p-toluenesulphonic acid); and salts with an amino acid, such as glutamic acid and aspartic acid.

The compounds of the present invention may contain several asymmetric carbon atoms in their molecules, and can thus form optical isomers which may have the (R)-configuration or the (S)-configuration. Also, because of the carbon-carbon double bond, they can exist in the form of geometric isomers, i.e. the (Z)-isomer or the (E)-isomer. Although these isomers are all represented herein by a single molecular formula, the present invention includes both the individual, isolated isomers and mixtures, including racemates, thereof. Where stereospecific synthesis techniques are employed, individual isomers may be prepared directly; on the other hand, if a mixture of isomers is prepared, the individual isomers may be obtained by conventional resolution techniques.

A preferred class of compounds of the present invention are those compounds in which:

R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,

in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a'), defined below, or an aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (a'), defined below;

R⁴ represents an unsubstituted phenyl group or a substituted phenyl group having from 1 to 5 of substituents (a'), defined below, and/or substituents (b), defined above;

substituents (a'):

C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; hydroxy groups; C₁ - C₄ alkylenedioxy groups; halogen atoms; and nitro groups.

A more preferred class of compounds of the present invention are those in which:

R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,

in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a''), defined below, or an unsubstituted aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or sulphur hetero-atoms;

R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;

A represents a 1,4-piperazin-1,4-diyl group;

B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;

R⁴ represents a substituted phenyl group having from 1 to 5 of substituents (a''), defined below; and

substituents (a''):

C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; C₁ - C₄ alkylenedioxy groups; and halogen atoms.

A still more preferred class of compounds of the present invention are those in which:

at least one of R¹ and R² represents an aryl group which is substituted by at least one of substituents (a'''), defined above;

R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

X represents an oxygen atom;

A represents a 1,4-piperazin-1,4-diyl group; and

B represents a carbonyl group.

Of the compounds of the present invention, the following are preferred:

(1) Compounds in which R¹ and R² are the same or different and each is represented by -R⁵ (in which R⁵ is as defined above);

(2) Compounds in which at least one of R¹ and R² represents an aryl group which is substituted by at least one of substituents (a), defined above;

(3) Compounds in which R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;

(4) Compounds in which R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

(5) Compounds in which X represents an oxygen atom;

(6) Compounds in which A represents a 1,4-piperazin-1,4-diyl group.

More preferred are those compounds in which R¹ and R² are as defined in (1) or (2) above, R³ is as defined in (3) above, R⁴ is as defined in (4) above, X is as defined in (5) above and A is as defined in (6)

above.

Still more preferred are those compounds in which:

(7) R¹ represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or halogen substituent;

5 (8) R¹ represents a substituted phenyl group having at least one C₁ - C₆ alkyl and/or C₁ - C₆ alkoxy and/or halogen substituent;

(9) R² represents an unsubstituted phenyl group or a substituted phenyl group which is substituted by at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or C₁ - C₆ haloalkyl and/or halogen substituent;

10 (10) R² represents a substituted phenyl group which is substituted by at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or C₁ - C₆ haloalkyl and/or halogen substituent;

(11) R² represents a substituted phenyl group which is substituted by at least one C₁ - C₂₂ alkyl and/or C₁ - C₆ haloalkyl and/or halogen substituent;

(12) R² represents a substituted phenyl group which is substituted by at least one C₁ - C₆ alkyl and/or C₁ - C₆ haloalkyl and/or halogen substituent;

15 (13) R² is as defined in any one of (10) to (12) above in which the substituent is at the meta position;

(14) R³ represents a hydrogen atom;

(15) R⁴ represents a substituted phenyl group having from 1 to 3 C₁ - C₆ alkoxy substituents, more especially from 1 to 3 C₁ - C₃ alkoxy substituents and most especially from 1 to 3 methoxy substituents;

(16) B represents a carbonyl group.

20 Most preferred are those compounds in which R¹ is as defined in (7) or (8) above, R² is as defined in any one of (9) to (13) above, R³ is as defined in (14) above, R⁴ is as defined in (15) above, B is as defined in (16) above, X is as defined in (5) above and A is as defined in (6) above.

25 Examples of specific compounds of the invention are given in the following formulae (I-1) to (I-3), in which the substituents are as defined in the corresponding one of Tables 1 to 3 [i.e. Table 1 relates to formula (I-1), Table 2 relates to formula (I-2) and so on]. In the Tables, the following abbreviations are used:

Bu butyl

iBu isobutyl

sBu sec-butyl

Et ethyl

30 Hx hexyl

Me methyl

Np naphthyl

Ph phenyl

Pn pentyl

35 Pr propyl

Pyr pyridyl

Quin quinolyl

Tfm trifluoromethyl Thi thienyl

40

45

50

55

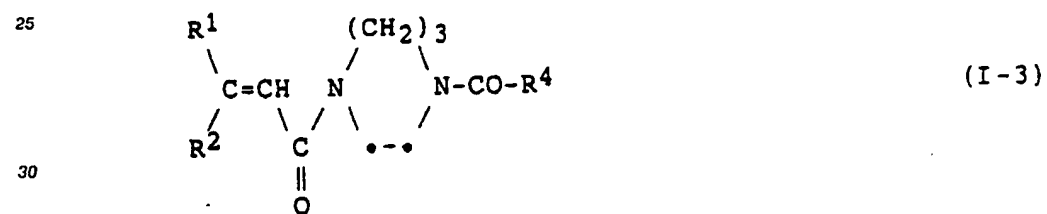
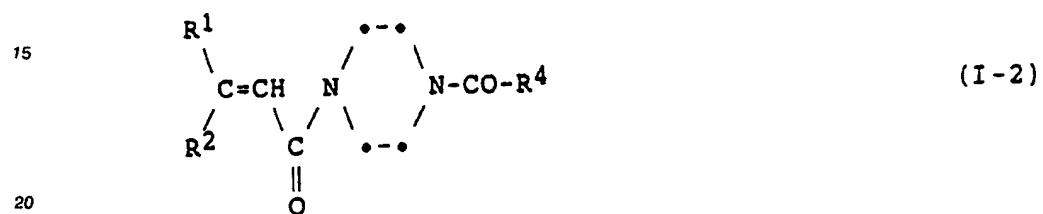
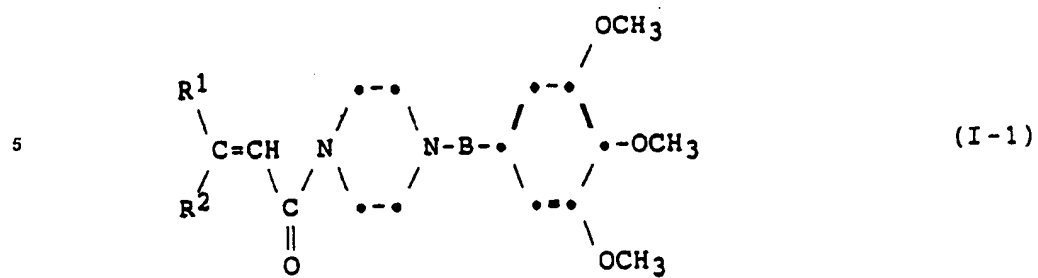


Table 1

5	Compound No.	R ¹	R ²	B
10	1-1	Ph	Ph	C=O
	1-2	4-MeOPh	4-MeOPh	C=O
	1-3	4-ClPh	4-ClPh	C=O
15	1-4	2-Thi	2-Thi	C=O
	1-5	4-Pyr	4-Pyr	C=O
	1-6	2-Np	2-Np	C=O
	1-7	1-Np	1-Np	C=O
20	1-8	3-Pyr	3-Pyr	C=O
	1-9	2-Pyr	2-Pyr	C=O
	1-10	2-Quin	2-Quin	C=O
25	1-11	PhC=C-	PhC=C-	C=O
	1-12	PhCH=CH-	PhCH=CH-	C=O
	1-13	3-Thi	3-Thi	C=O
30	1-14	3, 4-diMeOPh	3, 4-diMeOPh	C=O
	1-15	3, 4, 5-TriMeOPh	3, 4, 5-TriMeOPh	C=O
	1-16	Ph	4-MeOPh	C=O
	1-17	Ph	4-ClPh	C=O
35	1-18	Ph	2-Thi	C=O
	1-19	Ph	4-Pyr	C=O
	1-20	Ph	2-Np	C=O
40	1-21	Ph	1-Np	C=O
	1-22	Ph	3-Pyr	C=O
	1-23	Ph	2-Pyr	C=O
45	1-24	Ph	2-Quin	C=O
	1-25	Ph	PhC=C-	C=O
	1-26	Ph	PhCH=CH-	C=O
	1-27	Ph	3-Thi	C=O
50	1-28	Ph	3, 4-diMeOPh	C=O
	1-29	Ph	3, 4, 5-TriMeOPh	C=O

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-30	4-MeOPh	4-ClPh	C=O
	1-31	4-MeOPh	2-Thi	C=O
	1-32	3-MeOPh	4-Pyr	C=O
15	1-33	4-MeOPh	2-Np	C=O
	1-34	4-MeOPh	1-Np	C=O
	1-35	4-MeOPh	3-Pyr	C=O
	1-36	4-MeOPh	2-Pyr	C=O
20	1-37	4-MeOPh	2-Quin	C=O
	1-38	4-MeOPh	PhC=C-	C=O
	1-39	4-MeOPh	PhCH=CH-	C=O
25	1-40	4-MeOPh	3-Thi	C=O
	1-41	4-MeOPh	3, 4-diMeOPh	C=O
	1-42	4-MeOPh	3, 4, 5-TriMeOPh	C=O
30	1-43	4-ClPh	2-Thi	C=O
	1-44	4-ClPh	4-Pyr	C=O
	1-45	4-ClPh	2-Np	C=O
	1-46	4-ClPh	1-Np	C=O
35	1-47	2-ClPh	3-Pyr	C=O
	1-48	3-ClPh	2-Pyr	C=O
	1-49	4-ClPh	2-Quin	C=O
40	1-50	4-ClPh	PhC=C-	C=O
	1-51	4-ClPh	PhCH=CH-	C=O
	1-52	4-ClPh	3-Thi	C=O
45	1-53	4-ClPh	3, 4-diMeOPh	C=O
	1-54	4-ClPh	3, 4, 5-TriMeOPh	C=O
	1-55	2-Thi	4-Pyr	C=O
	1-56	2-Thi	2-Np	C=O
50	1-57	2-Thi	1-Np	C=O
	1-58	2-Thi	3-Pyr	C=O

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-59	2-Thi	2-Pyr	C=O
	1-60	2-Thi	2-Quin	C=O
	1-61	2-Thi	PhC=C-	C=O
15	1-62	2-Thi	PhCH=CH-	C=O
	1-63	2-Thi	3-Thi	C=O
	1-64	2-Thi	3, 4-diMeOPh	C=O
	1-65	2-Thi	3, 4, 5-TriMeOPh	C=O
20	1-66	4-Pyr	2-Np	C=O
	1-67	4-Pyr	1-Np	C=O
	1-68	4-Pyr	3-Pyr	C=O
25	1-69	4-Pyr	2-Pyr	C=O
	1-70	4-Pyr	2-Quin	C=O
	1-71	4-Pyr	PhC=C-	C=O
30	1-72	4-Pyr	PhCH=CH-	C=O
	1-73	4-Pyr	3-Thi	C=O
	1-74	4-Pyr	3, 4-diMeOPh	C=O
	1-75	4-Pyr	3, 4, 5-TriMeOPh	C=O
35	1-76	2-Np	1-Np	C=O
	1-77	2-Np	3-Pyr	C=O
	1-78	2-Np	2-Pyr	C=O
40	1-79	2-Np	2-Quin	C=O
	1-80	2-Np	PhC=C-	C=O
	1-81	2-Np	PhCH=CH-	C=O
45	1-82	2-Np	3-Thi	C=O
	1-83	2-Np	3, 4-diMeOPh	C=O
	1-84	2-Np	3, 4, 5-TriMeOPh	C=O
	1-85	1-Np	3-Pyr	C=O
50	1-86	1-Np	2-Pyr	C=O
	1-87	1-Np	2-Quin	C=O

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-88	1-Np	PhC=C-	C=O
	1-89	1-Np	PhCH=CH-	C=O
	1-90	1-Np	3-Thi	C=O
15	1-91	1-Np	3, 4-diMeOPh	C=O
	1-92	1-Np	3, 4, 5-TriMeOPh	C=O
	1-93	3-Pyr	2-Pyr	C=O
	1-94	3-Pyr	2-Quin	C=O
20	1-95	3-Pyr	PhC=C-	C=O
	1-96	3-Pyr	PhCH=CH-	C=O
	1-97	3-Pyr	3-Thi	C=O
25	1-98	3-Pyr	3, 4-diMeOPh	C=O
	1-99	3-Pyr	3, 4, 5-TriMeOPh	C=O
	1-100	2-Pyr	2-Quin	C=O
30	1-101	3-Pyr	PhC=C-	C=O
	1-102	2-Pyr	PhCH=CH-	C=O
	1-103	3-Pyr	3-Thi	C=O
	1-104	2-Quin	PhC=C-	C=O
35	1-105	2-Quin	PhCH=CH-	C=O
	1-106	2-Quin	3-Thi	C=O
	1-107	2-Quin	3, 4-diMeOPh	C=O
40	1-108	2-Quin	3, 4, 5-TriMeOPh	C=O
	1-109	PhC=C-	PhCH=CH-	C=O
	1-110	PhC=C-	3-Thi	C=O
45	1-111	PhC=C-	3, 4-diMeOPh	C=O
	1-112	PhC=C-	3, 4, 5-TriMeOPh	C=O
	1-113	PhCH=CH-	3-Thi	C=O
	1-114	PhCH=CH-	3, 4-diMeOPh	C=O
50	1-115	PhCH=CH-	3, 4, 5-TriMeOPh	C=O
	1-116	Ph	Ph	C=S

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-117	4-MeOPh	4-MeOPh	C=S
	1-118	4-ClPh	4-ClPh	C=S
	1-119	2-Thi	2-Thi	C=S
15	1-120	4-FPh	4-FPh	C=S
	1-121	2-Np	2-Np	C=S
	1-122	1-Np	1-Np	C=S
20	1-123	3-Pyr	3-Pyr	C=S
	1-124	2-Pyr	2-Pyr	C=S
	1-125	2-Quin	2-Quin	C=S
	1-126	PhC=C-	PhC=C-	C=S
25	1-127	PhCH=CH-	PhCH=CH-	C=S
	1-128	3-Thi	3-Thi	C=S
	1-129	Ph	4-MeOPh	C=S
30	1-130	Ph	4-ClPh	C=S
	1-131	Ph	2-Thi	C=S
	1-132	Ph	4-Pyr	C=S
	1-133	Ph	2-Np	C=S
35	1-134	Ph	1-Np	C=S
	1-135	Ph	3-Pyr	C=S
	1-136	Ph	2-Pyr	C=S
40	1-137	Ph	2-Quin	C=S
	1-138	Ph	PhC=C-	C=S
	1-139	Ph	PhCH=CH-	C=S
45	1-140	Ph	3-Thi	C=S
	1-141	4-MeOPh	4-ClPh	C=S
	1-142	2-MeOPh	2-Thi	C=S
	1-143	3-MeOPh	4-Pyr	C=S
50	1-144	4-MeOPh	2-Np	C=S
	1-145	4-MeOPh	1-Np	C=S

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-146	4-MeOPh	3-Pyr	C=S
	1-147	4-MeOPh	2-Pyr	C=S
	1-148	4-MeOPh	2-Quin	C=S
	1-149	4-MeOPh	PhC=C-	C=S
15	1-150	4-MeOPh	PhCH=CH-	C=S
	1-151	4-MeOPh	3-Thi	C=S
	1-152	4-C ₆ H ₅	2-Thi	C=S
20	1-153	4-C ₆ H ₅	4-Pyr	C=S
	1-154	3-C ₆ H ₅	2-Np	C=S
	1-155	3-C ₆ H ₅	1-Np	C=S
25	1-156	2-C ₆ H ₅	3-Pyr	C=S
	1-157	3-C ₆ H ₅	2-Pyr	C=S
	1-158	4-C ₆ H ₅	2-Quin	C=S
	1-159	4-C ₆ H ₅	PhC=C-	C=S
30	1-160	4-C ₆ H ₅	PhCH=CH-	C=S
	1-161	4-C ₆ H ₅	3-Thi	C=S
	1-162	2-Thi	4-Pyr	C=S
35	1-163	2-Thi	2-Np	C=S
	1-164	2-Thi	1-Np	C=S
	1-165	2-Thi	3-Pyr	C=S
40	1-166	2-Thi	2-Pyr	C=S
	1-167	2-Thi	2-Quin	C=S
	1-168	2-Thi	PhC=C-	C=S
	1-169	2-Thi	PhCH=CH-	C=S
45	1-170	2-Thi	3-Thi	C=S
	1-171	4-Pyr	2-Np	C=S
	1-172	4-Pyr	1-Np	C=S
50	1-173	4-Pyr	3-Pyr	C=S
	1-174	4-Pyr	2-Pyr	C=S

55

Table 1 (continued)

	Compound No.	R ¹	R ²	B
5				
10	1-175	4-Pyr	2-Quin	C=S
	1-176	4-Pyr	PhC=C-	C=S
	1-177	4-Pyr	PhCH=CH-	C=S
15	1-178	4-Pyr	3-Thi	C=S
	1-179	2-Np	1-Np	C=S
	1-180	2-Np	3-Pyr	C=S
	1-181	2-Np	2-Pyr	C=S
20	1-182	2-Np	2-Quin	C=S
	1-183	2-Np	PhC=C-	C=S
	1-184	2-Np	PhCH=CH-	C=S
25	1-185	2-Np	3-Thi	C=S
	1-186	1-Np	3-Pyr	C=S
	1-187	1-Np	2-Pyr	C=S
30	1-188	1-Np	2-Quin	C=S
	1-189	1-Np	PhC=C-	C=S
	1-190	1-Np	PhCH=CH-	C=S
	1-191	1-Np	3-Thi	C=S
35	1-192	3-Pyr	2-Pyr	C=S
	1-193	3-Pyr	2-Quin	C=S
	1-194	3-Pyr	PhC=C-	C=S
40	1-195	3-Pyr	PhCH=CH-	C=S
	1-196	3-Pyr	3-Thi	C=S
	1-197	2-Pyr	2-Quin	C=S
45	1-198	3-Pyr	PhC=C-	C=S
	1-199	2-Pyr	PhCH=CH-	C=S
	1-200	3-Pyr	3-Thi	C=S
	1-201	2-Quin	PhC=C-	C=S
50	1-202	2-Quin	PhCH=CH-	C=S
	1-203	2-Quin	3-Thi	C=S
55				

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-204	PhC=C-	PhCH=CH-	C=S
	1-205	PhC=C-	3-Thi	C=S
	1-206	PhCH=CH-	3-Thi	C=S
15	1-207	Ph	Ph	SO ₂
	1-208	4-MeOPh	4-MeOPh	SO ₂
	1-209	4-ClPh	4-ClPh	SO ₂
	1-210	2-Thi	2-Thi	SO ₂
20	1-211	4-Pyr	4-Pyr	SO ₂
	1-212	2-Np	2-Np	SO ₂
	1-213	1-Np	1-Np	SO ₂
25	1-214	3-Pyr	3-Pyr	SO ₂
	1-215	2-Pyr	2-Pyr	SO
	1-216	2-Quin	2-Quin	SO ₂
30	1-217	PhC=C-	PhC=C-	SO ₂
	1-218	PhCH=CH-	PhCH=CH-	SO ₂
	1-219	3-Thi	3-Thi	SO ₂
	1-220	Ph	4-MeOPh	SO ₂
35	1-221	Ph	4-ClPh	SO ₂
	1-222	Ph	2-Thi	SO ₂
	1-223	Ph	4-Pyr	SO ₂
40	1-224	Ph	2-Np	SO ₂
	1-225	Ph	1-Np	SO ₂
	1-226	Ph	3-Pyr	SO ₂
45	1-227	Ph	2-Pyr	SO ₂
	1-228	Ph	2-Quin	SO ₂
	1-229	Ph	PhC=C-	SO ₂
	1-230	Ph	PhCH=CH-	SO ₂
50	1-231	Ph	3-Thi	SO ₂
	1-232	4-MeOPh	4-ClPh	SO ₂

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-233	2-MeOPh	2-Thi	SO ₂
	1-234	3-MeOPh	4-Pyr	SO ₂
	1-235	4-MeOPh	2-Np	SO ₂
15	1-236	4-MeOPh	1-Np	SO ₂
	1-237	4-MeOPh	3-Pyr	SO
	1-238	4-MeOPh	2-Pyr	SO ₂
	1-239	4-MeOPh	2-Quin	SO ₂
20	1-240	4-MeOPh	PhC=C-	SO ₂
	1-241	4-MeOPh	PhCH=CH-	SO ₂
	1-242	4-MeOPh	3-Thi	SO ₂
25	1-243	4-ClPh	2-Thi	SO ₂
	1-244	4-ClPh	4-Pyr	SO ₂
	1-245	4-ClPh	2-Np	SO ₂
30	1-246	4-ClPh	1-Np	SO
	1-247	2-ClPh	3-Pyr	SO ₂
	1-248	3-ClPh	2-Pyr	SO ₂
	1-249	4-ClPh	2-Quin	SO ₂
35	1-250	4-ClPh	PhC=C-	SO ₂
	1-251	4-ClPh	PhCH=CH-	SO ₂
	1-252	4-ClPh	3-Thi	SO ₂
40	1-253	2-Thi	4-Pyr	SO ₂
	1-254	2-Thi	2-Np	SO ₂
	1-255	2-Thi	1-Np	SO ₂
45	1-256	2-Thi	3-Pyr	SO
	1-257	2-Thi	2-Pyr	SO ₂
	1-258	2-Thi	2-Quin	SO ₂
	1-259	2-Thi	PhC=C-	SO ₂
50	1-260	2-Thi	PhCH=CH-	SO ₂
	1-261	2-Thi	3-Thi	SO ₂

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-262	4-Pyr	2-Np	SO ₂
	1-263	4-Pyr	1-Np	SO ₂
	1-264	4-Pyr	3-Pyr	SO ₂
15	1-265	4-Pyr	2-Pyr	SO ₂
	1-266	4-Pyr	2-Quin	SO ₂
	1-267	4-Pyr	PhC=C-	SO ₂
	1-268	4-Pyr	PhCH=CH-	SO
20	1-269	4-Pyr	3-Thi	SO ₂
	1-270	2-Np	1-Np	SO ₂
	1-271	2-Np	3-Pyr	SO ₂
25	1-272	2-Np	2-Pyr	SO ₂
	1-273	2-Np	2-Quin	SO ₂
	1-274	2-Np	PhC=C-	SO ₂
30	1-275	2-Np	PhCH=CH-	SO ₂
	1-276	2-Np	3-Thi	SO ₂
	1-277	1-Np	3-Pyr	SO ₂
	1-278	1-Np	2-Pyr	SO ₂
35	1-279	1-Np	2-Quin	SO ₂
	1-280	1-Np	PhC=C-	SO ₂
	1-281	1-Np	PhCH=CH-	SO
40	1-282	1-Np	3-Thi	SO ₂
	1-283	3-Pyr	2-Pyr	SO ₂
	1-284	3-Pyr	2-Quin	SO ₂
45	1-285	3-Pyr	PhC=C-	SO ₂
	1-286	3-Pyr	PhCH=CH-	SO ₂
	1-287	3-Pyr	3-Thi	SO ₂
	1-288	2-Pyr	2-Quin	SO ₂
50	1-289	3-Pyr	PhC=C-	SO ₂
	1-290	2-Pyr	PhCH=CH-	SO ₂

55

Table 1 (continued)

Compound No.	R ¹	R ²	B
1-291	3-Pyr	3-Thi	SO ₂
1-292	2-Quin	PhC=C-	SO ₂
1-293	2-Quin	PhCH=CH-	SO ₂
1-294	2-Quin	3-Thi	SO ₂
1-295	PhC=C-	PhCH=CH-	SO ₂
1-296	PhC=C-	3-Thi	SO ₂
1-297	PhCH=CH-	3-Thi	SO ₂
1-298	Ph	Ph	CH ₂
1-299	4-MeOPh	4-MeOPh	CH ₂
1-300	4-ClPh	4-ClPh	CH ₂
1-301	2-Thi	2-Thi	CH ₂
1-302	4-Pyr	4-Pyr	CH ₂
1-303	2-Np	2-Np	CH ₂
1-304	1-Np	1-Np	CH ₂
1-305	3-Pyr	3-Pyr	CH ₂
1-306	2-Pyr	2-Pyr	CH ₂
1-307	2-Quin	2-Quin	CH ₂
1-308	PhC=C-	PhC=C-	CH ₂
1-309	PhCH=CH-	PhCH=CH-	CH ₂
1-310	3-Thi	3-Thi	CH ₂
1-311	3, 4-diMeOPh	3, 4-diMeOPh	CH ₂
1-312	3, 4, 5-TriMeOPh	3, 4, 5-TriMeOPh	CH ₂
1-313	Ph	4-MeOPh	CH ₂
1-314	Ph	4-ClPh	CH ₂
1-315	Ph	2-Thi	CH ₂
1-316	Ph	4-Pyr	CH ₂
1-317	Ph	2-Np	CH ₂
1-318	Ph	1-Np	CH ₂
1-319	Ph	3-Pyr	CH ₂

Table 1 (continued)

Compound No.	R ¹	R ²	B
10 1-320	Ph	2-Pyr	CH ₂
1-321	Ph	2-Quin	CH ₂
1-322	Ph	PhC=C-	CH ₂
15 1-323	Ph	PhCH=CH-	CH ₂
1-324	Ph	3-Thi	CH ₂
1-325	Ph	3, 4-diMeOPh	CH ₂
1-326	Ph	3, 4, 5-TriMeOPh	CH ₂
20 1-327	4-MeOPh	4-CiPh	CH ₂
1-328	2-MeOPh	2-Thi	CH ₂
1-329	3-MeOPh	4-Pyr	CH ₂
25 1-330	4-MeOPh	2-Np	CH ₂
1-331	4-MeOPh	1-Np	CH ₂
1-332	4-MeOPh	3-Pyr	CH ₂
30 1-333	4-MeOPh	2-Pyr	CH ₂
1-334	4-MeOPh	2-Quin	CH ₂
1-335	4-MeOPh	PhC=C-	CH ₂
1-336	4-MeOPh	PhCH=CH-	CH ₂
35 1-337	4-MeOPh	3-Thi	CH ₂
1-338	4-MeOPh	3, 4-diMeOPh	CH ₂
1-339	4-MeOPh	3, 4, 5-TriMeOPh	CH ₂
40 1-340	4-CiPh	2-Thi	CH ₂
1-341	4-CiPh	4-Pyr	CH ₂
1-342	3-CiPh	2-Np	CH ₂
45 1-343	3-CiPh	1-Np	CH ₂
1-344	2-CiPh	3-Pyr	CH ₂
1-345	3-CiPh	2-Pyr	CH ₂
1-346	4-CiPh	2-Quin	CH ₂
50 1-347	4-CiPh	PhC=C-	CH ₂
1-348	4-CiPh	PhCH=CH-	CH ₂

55

Table 1 (continued)

	Compound No.	R ¹	R ²	B
5				
10	1-349	4-ClPh	3-Thi	CH ₂
	1-350	4-ClPh	3, 4-diMeOPh	CH ₂
	1-351	4-ClPh	3, 4, 5-TriMeOPh	CH ₂
15	1-352	2-Thi	4-Pyr	CH ₂
	1-353	2-Thi	2-Np	CH ₂
	1-354	2-Thi	1-Np	CH ₂
	1-355	2-Thi	3-Pyr	CH ₂
20	1-356	2-Thi	2-Pyr	CH ₂
	1-357	2-Thi	2-Quin	CH ₂
	1-358	2-Thi	PhC=C-	CH ₂
25	1-359	2-Thi	PhCH=CH-	CH ₂
	1-360	2-Thi	3-Thi	CH ₂
	1-361	2-Thi	3, 4-diMeOPh	CH ₂
30	1-362	2-Thi	3, 4, 5-TriMeOPh	CH ₂
	1-363	4-Pyr	2-Np	CH ₂
	1-364	4-Pyr	1-Np	CH ₂
	1-365	4-Pyr	3-Pyr	CH ₂
35	1-366	4-Pyr	2-Pyr	CH ₂
	1-367	4-Pyr	2-Quin	CH ₂
	1-368	4-Pyr	PhC=C-	CH ₂
40	1-369	4-Pyr	PhCH=CH-	CH ₂
	1-370	4-Pyr	3-Thi	CH ₂
	1-371	4-Pyr	3, 4-diMeOPh	CH ₂
45	1-372	4-Pyr	3, 4, 5-TriMeOPh	CH ₂
	1-373	2-Np	1-Np	CH ₂
	1-374	2-Np	3-Pyr	CH ₂
	1-375	2-Np	2-Pyr	CH ₂
50	1-376	2-Np	2-Quin	CH ₂
	1-377	2-Np	PhC=C-	CH ₂

55

Table 1 (continued)

	Compound No.	R ¹	R ²	B
5				
10	1-378	2-Np	PhCH=CH-	CH ₂
	1-379	2-Np	3-Thi	CH ₂
	1-380	2-Np	3, 4-diMeOPh	CH ₂
15	1-381	2-Np	3, 4, 5-TriMeOPh	CH ₂
	1-382	1-Np	3-Pyr	CH ₂
	1-383	1-Np	2-Pyr	CH ₂
	1-384	1-Np	2-Quin	CH ₂
20	1-385	1-Np	PhC=C-	CH ₂
	1-386	1-Np	PhCH=CH-	CH ₂
	1-387	1-Np	3-Thi	CH ₂
25	1-388	1-Np	3, 4-diMeOPh	CH ₂
	1-389	1-Np	3, 4, 5-TriMeOPh	CH ₂
	1-390	3-Pyr	2-Pyr	CH ₂
30	1-391	3-Pyr	2-Quin	CH ₂
	1-392	3-Pyr	PhC=C-	CH ₂
	1-393	3-Pyr	PhCH=CH-	CH ₂
	1-394	3-Pyr	3-Thi	CH ₂
35	1-395	3-Pyr	3, 4-diMeOPh	CH ₂
	1-396	3-Pyr	3, 4, 5-TriMeOPh	CH ₂
	1-397	2-Pyr	2-Quin	CH ₂
40	1-398	3-Pyr	PhC=C-	CH ₂
	1-399	2-Pyr	PhCH=CH-	CH ₂
	1-400	3-Pyr	3-Thi	CH ₂
45	1-401	2-Quin	PhC=C-	CH ₂
	1-402	2-Quin	PhCH=CH-	CH ₂
	1-403	2-Quin	3-Thi	CH ₂
	1-404	2-Quin	3, 4-diMeOPh	CH ₂
50	1-405	2-Quin	3, 4, 5-TriMeOPh	CH ₂
	1-406	PhC=C-	PhCH=CH-	CH ₂

55

Table 1 (continued)

Compound No.	R ¹	R ²	B
1-407	PhC=C-	3-Thi	CH ₂
1-408	PhC=C-	3,4-diMeOPh	CH ₂
1-409	PhC=C-	3,4,5-TriMeOPh	CH ₂
1-410	PhCH=CH-	3-Thi	CH ₂
1-411	3-MeOPh	3-MeOPh	C=O
1-412	3-MeOPh	4-MeOPh	C=O
1-413	2-MeOPh	2-MeOPh	C=O
1-414	2-MeOPh	3-MeOPh	C=O
1-415	2-MeOPh	4-MeOPh	C=O
1-416	2-ClPh	2-ClPh	C=O
1-417	2-ClPh	3-ClPh	C=O
1-418	2-ClPh	4-ClPh	C=O
1-419	3-ClPh	3-ClPh	C=O
1-420	3-ClPh	4-ClPh	C=O
1-421	2-MePh	2-MePh	C=O
1-422	2-MePh	3-MePh	C=O
1-423	2-MePh	4-MePh	C=O
1-424	3-MePh	3-MePh	C=O
1-425	3-MePh	4-MePh	C=O
1-426	3-TfmPh	3-TfmPh	C=O
1-427	3-TfmCH ₂ Ph	3-TfmCH ₂ Ph	C=O
1-428	2-PrOPh	2-PrOPh	C=O
1-429	2-PrOPh	3-PrOPh	C=O
1-430	2-PrOPh	4-PrOPh	C=O
1-431	3-PrOPh	3-PrOPh	C=O
1-432	3-PrOPh	4-PrOPh	C=O
1-433	4-PrOPh	4-PrOPh	C=O
1-434	3-sBuOPh	3-sBuOPh	C=O
1-435	4-sBuOPh	4-sBuOPh	C=O

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-436	3- <u>i</u> BuOPh	3- <u>i</u> BuOPh	C=O
	1-437	4- <u>i</u> BuOPh	4- <u>i</u> BuOPh	C=O
	1-438	2-EtPh	2-EtPh	C=O
15	1-439	2-EtPh	3-EtPh	C=O
	1-440	2-EtPh	4-EtPh	C=O
	1-441	3-EtPh	3-EtPh	C=O
	1-442	3-EtPh	4-EtPh	C=O
20	1-443	4-EtPh	4-EtPh	C=O
	1-444	2-PrPh	2-PrPh	C=O
	1-445	2-PrPh	3-PrPh	C=O
25	1-446	2-PrPh	4-PrPh	C=O
	1-447	3-PrPh	3-PrPh	C=O
	1-448	3-PrPh	4-PrPh	C=O
30	1-449	4-PrPh	4-PrPh	C=O
	1-450	3- <u>i</u> BuPh	3- <u>i</u> BuPh	C=O
	1-451	3- <u>i</u> BuPh	4- <u>i</u> BuPh	C=O
	1-452	2-ClPh	Ph	C=O
35	1-453	2-ClPh	3-MeOPh	C=O
	1-454	2-ClPh	4-MeOPh	C=O
	1-455	2-ClPh	3-PrOPh	C=O
40	1-456	2-ClPh	4-PrOPh	C=O
	1-457	2-ClPh	3-BuOPh	C=O
	1-458	2-ClPh	4-BuOPh	C=O
45	1-459	2-ClPh	3-MePh	C=O
	1-460	2-ClPh	4-MePh	C=O
	1-461	2-ClPh	3-TfmPh	C=O
	1-462	2-ClPh	3, 4-diMeOPh	C=O
50	1-463	2-ClPh	3-MeO-4-PrOPh	C=O
	1-464	2-ClPh	3, 4-diPrOPh	C=O

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-465	2-ClPh	3, 4-diClPh	C=O
	1-466	3-ClPh	Ph	C=O
	1-467	3-ClPh	3-MeOPh	C=O
	1-468	3-ClPh	4-MeOPh	C=O
15	1-469	3-ClPh	3-PrOPh	C=O
	1-470	3-ClPh	4-PrOPh	C=O
	1-471	3-ClPh	3- <u>i</u> BuOPh	C=O
20	1-472	3-ClPh	4- <u>i</u> BuOPh	C=O
	1-473	3-ClPh	2-MePh	C=O
	1-474	3-ClPh	3-MePh	C=O
25	1-475	3-ClPh	4-MePh	C=O
	1-476	3-ClPh	3-TfmPh	C=O
	1-477	3-ClPh	3-EtPh	C=O
	1-478	3-ClPh	4-EtPh	C=O
30	1-479	3-ClPh	3-PrPh	C=O
	1-480	3-ClPh	4-PrPh	C=O
	1-481	3-ClPh	2, 3-diMeOPh	C=O
35	1-482	3-ClPh	3, 4-diMeOPh	C=O
	1-483	3-ClPh	4-MeO-3-PrOPh	C=O
	1-484	3-ClPh	3, 4-diPrOPh	C=O
40	1-485	3-ClPh	2, 3-diClPh	C=O
	1-486	3-ClPh	3, 4-diClPh	C=O
	1-487	4-ClPh	3-MeOPh	C=O
45	1-488	4-ClPh	4-MeOPh	C=O
	1-489	4-ClPh	3-PrOPh	C=O
	1-490	4-ClPh	4-PrOPh	C=O
	1-491	4-ClPh	3- <u>i</u> BuOPh	C=O
50	1-492	4-ClPh	4- <u>i</u> BuOPh	C=O
	1-493	4-ClPh	2, 3-diClPh	C=O

55

Table 1 (continued)

Compound No.	R ¹	R ²	B
1-494	2, 3-diC ₆ H ₄	Ph	C=O
1-495	2, 3-diC ₆ H ₄	3-MeOPh	C=O
1-496	2, 3-diC ₆ H ₄	4-MeOPh	C=O
1-497	2, 3-diC ₆ H ₄	3-PrOPh	C=O
1-498	2, 3-diC ₆ H ₄	4-PrOPh	C=O
1-499	2, 3-diC ₆ H ₄	3- <u>s</u> BuOPh	C=O
1-500	2, 3-diC ₆ H ₄	4- <u>s</u> BuOPh	C=O
1-501	2, 3-diC ₆ H ₄	3, 4-diMeOPh	C=O
1-502	2, 3-diC ₆ H ₄	3-MePh	C=O
1-503	2, 3-diC ₆ H ₄	4-MePh	C=O
1-504	2, 3-diC ₆ H ₄	3-EtPh	C=O
1-505	2, 3-diC ₆ H ₄	4-EtPh	C=O
1-506	2, 3-diC ₆ H ₄	3-PrPh	C=O
1-507	2, 3-diC ₆ H ₄	4-PrPh	C=O
1-508	2, 3-diC ₆ H ₄	3- <u>i</u> BuOPh	C=O
1-509	2, 3-diC ₆ H ₄	4- <u>i</u> BuOPh	C=O
1-510	3, 4-diC ₆ H ₄	Ph	C=O
1-511	3, 4-diC ₆ H ₄	2-MeOPh	C=O
1-512	3, 4-diC ₆ H ₄	3-MeOPh	C=O
1-513	3, 4-diC ₆ H ₄	4-MeOPh	C=O
1-514	3, 4-diC ₆ H ₄	3-PrOPh	C=O
1-515	3, 4-diC ₆ H ₄	4-PrOPh	C=O
1-516	3, 4-diC ₆ H ₄	3- <u>i</u> BuOPh	C=O
1-517	3, 4-diC ₆ H ₄	4- <u>i</u> BuOPh	C=O
1-518	3, 4-diC ₆ H ₄	3-MePh	C=O
1-519	3, 4-diC ₆ H ₄	4-MePh	C=O
1-520	3, 4-diC ₆ H ₄	3-PrPh	C=O
1-521	3, 4-diC ₆ H ₄	4-PrPh	C=O
1-522	3, 4-diC ₆ H ₄	3- <u>i</u> BuPh	C=O

Tabl 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-523	3, 4-diC ₆ H ₅	4-iBuPh	C=O
	1-524	3-FPh	3-FPh	C=O
	1-525	4-FPh	4-FPh	C=O
15	1-526	4-FPh	Ph	C=O
	1-527	3-FPh	4-FPh	C=O
	1-528	3-FPh	3-MeOPh	C=O
	1-529	3-FPh	4-MeOPh	C=O
20	1-530	3-FPh	3-PrOPh	C=O
	1-531	3-FPh	4-PrOPh	C=O
	1-532	3-FPh	3-iBuOPh	C=O
25	1-533	3-FPh	4-iBuOPh	C=O
	1-534	3-FPh	3-MePh	C=O
	1-535	3-FPh	4-MePh	C=O
30	1-536	3-FPh	3, 4-diMePh	C=O
	1-537	3-FPh	3-TfmPh	C=O
	1-538	3-FPh	3-EtPh	C=O
	1-539	3-FPh	4-PrPh	C=O
35	1-540	3-FPh	4-iBuPh	C=O
	1-541	3-FPh	3, 4-diMeOPh	C=O
	1-542	3-FPh	2-C ₆ H ₅	C=O
40	1-543	3-FPh	3-C ₆ H ₅	C=O
	1-544	3-FPh	4-C ₆ H ₅	C=O
	1-545	3-FPh	2, 3-diC ₆ H ₅	C=O
45	1-546	3-FPh	3, 4-diC ₆ H ₅	C=O
	1-547	3-FPh	4-PrPh	C=O
	1-548	3-FPh	4-iBuPh	C=O
	1-549	4-FPh	Ph	C=O
50	1-550	4-FPh	3, 4-diC ₆ H ₅	C=O
	1-551	4-FPh	3, 4-diMeOPh	C=O

55

Table 1 (continued)

	Compound No.	R ¹	R ²	B
5				
10	1-552	4-FPh	3, 4, 5-triMeOPh	C=O
	1-553	4-FPh	3-MePh	C=O
	1-554	4-FPh	4-MePh	C=O
15	1-555	4-FPh	3, 4-diMePh	C=O
	1-556	3-TfmPh	Ph	C=O
	1-557	3-TfmPh	3-MeOPh	C=O
	1-558	3-TfmPh	4-MeOPh	C=O
20	1-559	3-TfmPh	3-PrOPh	C=O
	1-560	3-TfmPh	4-PrOPh	C=O
	1-561	3-TfmPh	3- <u>i</u> BuOPh	C=O
25	1-562	3-TfmPh	4- <u>i</u> BuOPh	C=O
	1-563	3-TfmPh	3-MePh	C=O
	1-564	3-TfmPh	4-MePh	C=O
30	1-565	3-TfmPh	2, 3-diMePh	C=O
	1-566	3-TfmPh	3, 4-diMePh	C=O
	1-567	3-TfmPh	3-EtPh	C=O
	1-568	3-TfmPh	4-EtPh	C=O
35	1-569	3-TfmPh	3-PrPh	C=O
	1-570	3-TfmPh	4-PrPh	C=O
	1-571	3-TfmPh	3- <u>i</u> BuPh	C=O
40	1-572	3-TfmPh	4- <u>i</u> BuPh	C=O
	1-573	3-TfmPh	2, 3-diMeOPh	C=O
	1-574	3-TfmPh	3, 4-diMeOPh	C=O
45	1-575	2-MePh	Ph	C=O
	1-576	2-MePh	3, 4-diMePh	C=O
	1-577	2-MePh	3, 4-diMeOPh	C=O
	1-578	2-MePh	3-PrPh	C=O
50	1-579	2-MePh	4- <u>i</u> BuPh	C=O
	1-580	3-MePh	Ph	C=O

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-581	3-MePh	1-Np	C=O
	1-582	3-MePh	2-Np	C=O
	1-583	3-MePh	3, 4-diMePh	C=O
	1-584	3-MePh	3-EtPh	C=O
15	1-585	3-MePh	4-EtPh	C=O
	1-586	3-MePh	3-PrPh	C=O
	1-587	3-MePh	4-PrPh	C=O
20	1-588	3-MePh	3- <u>i</u> BuPh	C=O
	1-589	3-MePh	4- <u>i</u> BuPh	C=O
	1-590	3-MePh	3, 4-diMeOPh	C=O
25	1-591	3-MePh	3-MeOPh	C=O
	1-592	3-MePh	4-MeOPh	C=O
	1-593	3-MePh	3-PrOPh	C=O
	1-594	3-MePh	4-PrOPh	C=O
30	1-595	3-MePh	3- <u>i</u> BuOPh	C=O
	1-596	3-MePh	4- <u>i</u> BuOPh	C=O
	1-597	4-MePh	Ph	C=O
35	1-598	4-MePh	3, 4-diMeOPh	C=O
	1-599	4-MePh	3-MeOPh	C=O
	1-600	4-MePh	4-MeOPh	C=O
40	1-601	4-MePh	3, 4-diPrOPh	C=O
	1-602	4-MePh	3-MeO-4-PrOPh	C=O
	1-603	3-MeO-4-PrOPh	Ph	C=O
	1-604	3-MeO-4-PrOPh	2-Np	C=O
45	1-605	3-MeO-4-PrOPh	3-Np	C=O
	1-606	3, 4-diPrOPh	Ph	C=O
	1-607	3-MeOPh	Ph	C=O
50	1-608	3-PrOPh	Ph	C=O
	1-609	4-PrOPh	Ph	C=O
55				

Tabl 1 (continu d)

Compound No.	R ¹	R ²	B
1-610	3- <u>i</u> BuOPh	Ph	C=O
1-611	4- <u>i</u> BuOPh	Ph	C=O
1-612	3-EtPh	Ph	C=O
1-613	3-EtPh	1-Np	C=O
1-614	3-EtPh	2-Np	C=O
1-615	3-PrPh	Ph	C=O
1-616	3-PrPh	1-Np	C=O
1-617	3-PrPh	2-Np	C=O
1-618	3- <u>i</u> BuPh	Ph	C=O
1-619	3- <u>i</u> BuPh	1-Np	C=O
1-620	3- <u>i</u> BuPh	2-Np	C=O
1-621	3,4-diMePh	Ph	C=O
1-622	Ph	3-MeO-4-EtOPh	C=O
1-623	Ph	3-MeO-4-EtOPh	C=S
1-624	Ph	3-MeO-4-EtOPh	CH ₂
1-625	Ph	3-MeO-4-PrOPh	C=S
1-626	Ph	3-MeO-4-PrOPh	CH ₂
1-627	Ph	3-MeO-4-BuOPh	C=O
1-628	Ph	3-MeO-4-PnOPh	C=O
1-629	Ph	3-MeO-4-HxOPh	C=O
1-630	Ph	3-EtO-4-MeOPh	C=O
1-631	Ph	3-PrO-4-MeOPh	C=O
1-632	Ph	3-BuO-4-MeOPh	C=O
1-633	Ph	3-PnO-4-MeOPh	C=O
1-634	Ph	3-HxO-4-MeOPh	C=O
1-635	Ph	3,4-diMeOPh	C=S
1-636	Ph	3,4-diMeOPh	CH ₂
1-637	Ph	3,4-diEtOPh	C=O
1-638	Ph	3,4-diPrOPh	C=S

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-639	Ph	3,4-diPrOPh	CH ₂
	1-640	Ph	3,4-diBuOPh	C=O
	1-641	Ph	4-EtOPh	C=O
	1-642	Ph	4-BuOPh	C=O
15	1-643	Ph	4-PnOPh	C=O
	1-644	Ph	4-HxOPh	C=O
	1-645	Ph	3-MeOPh	C=O
20	1-646	Ph	3-EtOPh	C=O
	1-647	Ph	3-BuOPh	C=O
	1-648	Ph	3-BuPh	C=O
25	1-649	Ph	4-BuPh	C=O
	1-650	Ph	3-PnPh	C=O
	1-651	Ph	3-HxPh	C=O
	1-652	Ph	3,4-diEtPh	C=O
30	1-653	Ph	3,4-diPrPh	C=O
	1-654	Ph	3,4-diBuPh	C=O
	1-655	3-BuOPh	3-BuOPh	C=O
35	1-656	4-ClPh	2,3-diMeOPh	C=O
	1-657	2,3-diClPh	3-BuPh	C=O
	1-658	2,3-diClPh	4-BuPh	C=O
	1-659	3,4-diClPh	3-EtPh	C=O
40	1-660	3,4-diClPh	4-EtPh	C=O
	1-661	3,4-diClPh	3-BuPh	C=O
	1-662	3,4-diClPh	4-BuPh	C=O
45	1-663	3,4-diClPh	4-MeOPh	C=S
	1-664	3,4-diClPh	4-MeOPh	CH ₂
	1-665	3,4-diClPh	4-PrOPh	C=S
50	1-666	3,4-diClPh	3-PrOPh	CH ₂
	1-667	3,4-diClPh	3-BuOPh	C=O

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-668	3, 4-diClPh	4-BuOPh	C=O
	1-669	3, 4-diClPh	3, 4-diMeOPh	C=O
	1-670	3-TfmPh	3-EtOPh	C=O
15	1-671	3-TfmPh	4-EtOPh	C=O
	1-672	3-TfmPh	3-BuOPh	C=O
	1-673	3-TfmPh	3-PnOPh	C=O
	1-674	3-TfmPh	3-HxOPh	C=O
20	1-675	3-TfmPh	4-BuOPh	C=O
	1-676	3-TfmPh	4-PnOPh	C=O
	1-677	3-TfmPh	4-HxOPh	C=O
25	1-678	3-TfmPh	4-BuPh	C=O
	1-679	3-TfmPh	3-EtO-4-MeOPh	C=O
	1-680	3-TfmPh	3-PrO-4-MeOPh	C=O
30	1-681	3-TfmPh	3-BuO-4-MeOPh	C=O
	1-682	3-TfmPh	3-PnO-4-MeOPh	C=O
	1-683	3-TfmPh	3-HxO-4-MeOPh	C=O
	1-684	3-TfmPh	3-MeO-4-EtOPh	C=O
35	1-685	3-TfmPh	3-MeO-4-PrOPh	C=O
	1-686	3-TfmPh	3-MeO-4-PrOPh	C=S
	1-687	3-TfmPh	3-MeO-4-PrOPh	CH ₂
40	1-688	3-TfmPh	3-MeO-4-BuOPh	C=O
	1-689	3-TfmPh	3-MeO-4-PnOPh	C=O
	1-690	3-TfmPh	3-MeO-4-HxOPh	C=O
45	1-691	3-TfmPh	3, 4-diMeOPh	C=S
	1-692	3-TfmPh	3, 4-diMeOPh	CH ₂
	1-693	3-TfmPh	3, 4-diEtOPh	C=O
	1-694	3-TfmPh	3, 4-diPrOPh	C=O
50	1-695	3-TfmPh	3, 4-diPrOPh	C=S
	1-696	3-TfmPh	3, 4-diPrOPh	CH ₂

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-697	3-TfmPh	3, 4-di BuOPh	C=O
	1-698	3-MePh	3-MePh	C=S
	1-699	3-MePh	3-MePh	CH ₂
	1-700	3-MePh	3-BuPh	C=O
15	1-701	3-MePh	4-BuPh	C=O
	1-702	3-MePh	3-EtOPh	C=O
	1-703	3-MePh	4-EtOPh	C=O
20	1-704	3-MePh	3-BuOPh	C=O
	1-705	3-MePh	3-PnOPh	C=O
	1-706	3-MePh	3-HxOPh	C=O
25	1-707	3-MePh	4-BuOPh	C=O
	1-708	3-MePh	4-PnOPh	C=O
	1-709	3-MePh	4-HxOPh	C=O
30	1-710	3-MePh	3-MeO-4-PrOPh	C=O
	1-711	3-MePh	3-MeO-4-PrOPh	C=S
	1-712	3-MePh	3-MeO-4-PrOPh	CH ₂
	1-713	3-MePh	3-MeO-4-EtOPh	C=O
35	1-714	3-MePh	3-MeO-4-BuOPh	C=O
	1-715	3-MePh	3-MeO-4-PnOPh	C=O
	1-716	3-MePh	3-MeO-4-HxOPh	C=O
40	1-717	3-MePh	3-EtO-4-MeOPh	C=O
	1-718	3-MePh	3-PrO-4-MeOPh	C=O
	1-719	3-MePh	3-BuO-4-MeOPh	C=O
	1-720	3-MePh	3-PnO-4-MeOPh	C=O
45	1-721	3-MePh	3-HxO-4-MeOPh	C=O
	1-722	3-MePh	3, 4-diMeOPh	C=S
	1-723	3-MePh	3, 4-diMeOPh	CH ₂
50	1-724	3-MePh	3, 4-diEtOPh	C=O
	1-725	3-MePh	3, 4-diPrOPh	C=O

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-726	3-MePh	3,4-diBuOPh	C=O
	1-727	3,4-methylenedioxyPh	Ph	C=O
	1-728	3,4-methylenedioxyPh	3-ClPh	C=O
15	1-729	3,4-methylenedioxyPh	3,4-diClPh	C=O
	1-730	3,4-methylenedioxyPh	3-MePh	C=O
	1-731	3,4-methylenedioxyPh	3-TfmPh	C=O
	1-732	3-ClPh	3-EtOPh	C=O
20	1-733	3-ClPh	4-EtOPh	C=O
	1-734	3-ClPh	3-BuOPh	C=O
	1-735	3-ClPh	3-PnOPh	C=O
25	1-736	3-ClPh	3-HxOPh	C=O
	1-737	3-ClPh	4-BuOPh	C=O
	1-738	3-ClPh	4-PnOPh	C=O
30	1-739	3-ClPh	4-HxOPh	C=O
	1-740	3-ClPh	3-MeO-4-PrOPh	C=O
	1-741	3-ClPh	3-MeO-4-PrOPh	C=S
	1-742	3-ClPh	3-MeO-4-PrOPh	CH ₂
35	1-743	3-ClPh	3-MeO-4-EtOPh	C=O
	1-744	3-ClPh	3-MeO-4-PnOPh	C=O
	1-745	3-ClPh	3-MeO-4-HxOPh	C=O
40	1-746	3-ClPh	3-EtO-4-MeOPh	C=O
	1-747	3-ClPh	3-BuO-4-MeOPh	C=O
	1-748	3-ClPh	3-PnO-4-MeOPh	C=O
	1-749	3-ClPh	3-HxO-4-MeOPh	C=O
45	1-750	3-ClPh	3,4-diMeOPh	C=S
	1-751	3-ClPh	3,4-diMeOPh	CH ₂
	1-752	3-ClPh	3,4-diEtOPh	C=O
50	1-753	3-ClPh	3,4-diPrOPh	C=S
	1-754	3-ClPh	3,4-diPrOPh	CH ₂

55

Table 1 (continued)

5	Compound No.	R ¹	R ²	B
10	1-755	3-ClPh	3, 4-diBuOPh	C=O
	1-756	3-ClPh	3-BuPh	C=O
	1-757	3-ClPh	4-BuPh	C=O
	1-758	1-Np	3-ClPh	C=O
15	1-759	2-Np	3-ClPh	C=O
	1-760	1-Np	3, 4-diClPh	C=O
	1-761	2-Np	3, 4-diClPh	C=O
20	1-762	1-Np	3-TfmPh	C=O
	1-763	2-Np	3-TfmPh	C=O
	1-764	3-BrPh	3-BrPh	C=O
25	1-765	3-BrPh	3-MeOPh	C=O
	1-766	3-BrPh	3-EtOPh	C=O
	1-767	3-BrPh	3-PrOPh	C=O
	1-768	3-BrPh	3-BuOPh	C=O
30	1-769	3-BrPh	3-PnOPh	C=O
	1-770	3-BrPh	3-HxOPh	C=O
	1-771	3-BrPh	4-MeOPh	C=O
35	1-772	3-BrPh	4-EtOPh	C=O
	1-773	3-BrPh	4-PrOPh	C=O
	1-774	3-BrPh	4-BuOPh	C=O
40	1-775	3-BrPh	4-PnOPh	C=O
	1-776	3-BrPh	4-HxOPh	C=O
	1-777	3-BrPh	3-MeO-4-EtOPh	C=O
	1-778	3-BrPh	3-MeO-4-PrOPh	C=O
45	1-779	3-BrPh	3-MeO-4-BuOPh	C=O
	1-780	3-BrPh	3-EtO-4-MeOPh	C=O
	1-781	3-BrPh	3-PrO-4-MeOPh	C=O
50	1-782	3-BrPh	3-BuO-4-MeOPh	C=O
	1-783	3-BrPh	3, 4-diEtOPh	C=O

55

Table 1 (continuation)

5	Compound No.	R ¹	R ²	B
10	1-784	3-BrPh	3,4-diPrOPh	C=O
	1-785	3-BrPh	3-MePh	C=O
	1-786	3-BrPh	3-EtPh	C=O
	1-787	3-BrPh	4-MePh	C=O
15	1-788	3-BrPh	4-EtPh	C=O
	1-789	3-BrPh	1-Np	C=O
	1-790	3-BrPh	2-Np	C=O
20	1-791	3,5-diC ₆ H ₄ Ph	3-MeOPh	C=O
	1-792	3,5-diC ₆ H ₄ Ph	3-PrOPh	C=O
	1-793	3,5-diC ₆ H ₄ Ph	4-MeOPh	C=O
25	1-794	3,5-diC ₆ H ₄ Ph	4-PrOPh	C=O
	1-795	3,5-diC ₆ H ₄ Ph	3-EtPh	C=O
	1-796	3,5-diC ₆ H ₄ Ph	4-EtPh	C=O
	1-797	3,5-diC ₆ H ₄ Ph	3-PrPh	C=O
30	1-798	3,5-diC ₆ H ₄ Ph	4-PrPh	C=O

35

40

45

50

55

Table 2

Compound No.	R ¹	R ²	R ⁴
2-1	3-ClPh	3-ClPh	3,4-diMeOPh
2-2	4-ClPh	4-ClPh	3,4-diMeOPh
2-3	3-ClPh	2,3-diClPh	3,4-diMeOPh
2-4	3-ClPh	3,4-diClPh	3,4-diMeOPh
2-5	4-ClPh	2,3-diClPh	3,4-diMeOPh
2-6	3-ClPh	3-MeOPh	3,4-diMeOPh
2-7	3-ClPh	4-MeOPh	3,4-diMeOPh
2-8	3-ClPh	3,4-diMeOPh	3,4-diMeOPh
2-9	3-ClPh	3-MeO-3-PrOPh	3,4-diMeOPh
2-10	2,3-diClPh	3-MeOPh	3,4-diMeOPh
2-11	2,3-diClPh	4-MeOPh	3,4-diMeOPh
2-12	2,3-diClPh	3-MePh	3,4-diMeOPh
2-13	2,3-diClPh	4-MePh	3,4-diMeOPh
2-14	3,4-diClPh	3-MeOPh	3,4-diMeOPh
2-15	3,4-diClPh	4-MeOPh	3,4-diMeOPh
2-16	3,4-diClPh	4-PrOPh	3,4-diMeOPh
2-17	3,4-diClPh	4- <u>i</u> BuOPh	3,4-diMeOPh
2-18	3,4-diClPh	3-MePh	3,4-diMeOPh
2-19	3,4-diClPh	4-MePh	3,4-diMeOPh
2-20	3,4-diClPh	4- <u>i</u> BuPh	3,4-diMeOPh
2-21	3-MePh	3-MePh	3,4-diMeOPh
2-22	3-MePh	4-MePh	3,4-diMeOPh
2-23	3-MePh	4-MeOPh	3,4-diMeOPh
2-24	3-MePh	3-PrOPh	3,4-diMeOPh
2-25	3-MePh	4-PrOPh	3,4-diMeOPh
2-26	3-MePh	3- <u>i</u> BuOPh	3,4-diMeOPh
2-27	3-MePh	4- <u>i</u> BuOPh	3,4-diMeOPh
2-28	3-MePh	3,4-diMePh	3,4-diMeOPh
2-29	3-MePh	3,4-diMeOPh	3,4-diMeOPh

Table 2 (continued)

Compound No.	R ¹	R ²	R ⁴
2-30	3-MePh	3,4-diPrOPh	3,4-diMeOPh
2-31	3-MePh	3-MeO-4-PrOPh	3,4-diMeOPh
2-32	3-TfmPh	3-ClPh	3,4-diMeOPh
2-33	3-TfmPh	4-ClPh	3,4-diMeOPh
2-34	3-TfmPh	3-MeOPh	3,4-diMeOPh
2-35	3-TfmPh	4-MeOPh	3,4-diMeOPh
2-36	3-TfmPh	3-PrOPh	3,4-diMeOPh
2-37	3-TfmPh	4-PrOPh	3,4-diMeOPh
2-38	3-TfmPh	3- <u>i</u> BuOPh	3,4-diMeOPh
2-39	3-TfmPh	4- <u>i</u> BuOPh	3,4-diMeOPh
2-40	3-TfmPh	3,4-diMeOPh	3,4-diMeOPh
2-41	3-ClPh	3-ClPh	3-MeOPh
2-42	3-ClPh	4-ClPh	3-MeOPh
2-43	3-ClPh	3-MeOPh	3-MeOPh
2-44	3-ClPh	4-MeOPh	3-MeOPh
2-45	3-ClPh	3,4-diMeOPh	3-MeOPh
2-46	3,4-diClPh	4-MeOPh	3-MeOPh
2-47	3,4-diClPh	4-PrOPh	3-MeOPh
2-48	3,4-diClPh	4- <u>i</u> BuOPh	3-MeOPh
2-49	3-MePh	3-MePh	3-MeOPh
2-50	3-MePh	4-MeOPh	3-MeOPh
2-51	3-MePh	4-PrOPh	3-MeOPh
2-52	3-MePh	4- <u>i</u> BuOPh	3-MeOPh
2-53	3-MePh	3,4-diMeOPh	3-MeOPh
2-54	3-MePh	3,4-diClPh	3-MeOPh
2-55	3-MePh	3,4-diMePh	3-MeOPh
2-56	3-TfmPh	4-MeOPh	3-MeOPh
2-57	3-TfmPh	4-PrOPh	3-MeOPh
2-58	3-TfmPh	4- <u>i</u> BuOPh	3-MeOPh

Table 2 (continued)

5	Compound No.	R ¹	R ²	R ⁴
10	2-59	3-TfmPh	3,4-diMeOPh	3-MeOPh
	2-60	3-TfmPh	3,4-diClPh	3-MeOPh
	2-61	3-TfmPh	3,4-diMePh	3-MeOPh
15	2-62	3-ClPh	3-ClPh	4-MeOPh
	2-63	3-ClPh	4-ClPh	4-MeOPh
	2-64	3-ClPh	3-MeOPh	4-MeOPh
	2-65	3-ClPh	4-MeOPh	4-MeOPh
20	2-66	3-ClPh	3,4-diMeOPh	4-MeOPh
	2-67	3,4-diClPh	4-MeOPh	4-MeOPh
	2-68	3,4-diClPh	4-PrOPh	4-MeOPh
25	2-69	3,4-diClPh	4-iBuOPh	4-MeOPh
	2-70	3-MePh	3-MePh	4-MeOPh
	2-71	3-MePh	4-MeOPh	4-MeOPh
30	2-72	3-MePh	4-PrOPh	4-MeOPh
	2-73	3-MePh	4-iBuOPh	4-MeOPh
	2-74	3-MePh	3,4-diMeOPh	4-MeOPh
	2-75	3-MePh	3,4-diClPh	4-MeOPh
35	2-76	3-MePh	3,4-diMePh	4-MeOPh
	2-77	3-TfmPh	4-MeOPh	4-MeOPh
	2-78	3-TfmPh	4-PrOPh	4-MeOPh
40	2-79	3-TfmPh	4-iBuOPh	4-MeOPh
	2-80	3-TfmPh	3,4-diMeOPh	4-MeOPh
	2-81	3-TfmPh	3,4-diClPh	4-MeOPh
45	2-82	3-TfmPh	3,4-diMePh	4-MeOPh
	2-83	Ph	3,4-diMeOPh	3,4-diMeOPh
	2-84	Ph	3,4-diMeOPh	3-MeOPh
	2-85	Ph	3,4-diMeOPh	4-MeOPh
50	2-86	Ph	3,4-diPrOPh	3,4-diMeOPh
	2-87	Ph	3,4-diPrOPh	3-M OP h

55

Table 2 (continued)

Compound No.	R ¹	R ²	R ⁴
2-88	Ph	3, 4-diPrOPh	4-MeOPh
2-89	Ph	3-MeO-4-PrOPh	3, 4-diMeOPh
2-90	Ph	3-MeO-4-PrOPh	3-MeOPh
2-91	Ph	3-MeO-4-PrOPh	4-MeOPh
2-92	3-ClPh	3, 4-diPrOPh	3, 4-diMeOPh
2-93	3-ClPh	3, 4-diPrOPh	3-MeOPh
2-94	3-ClPh	3, 4-diPrOPh	4-MeOPh
2-95	3-ClPh	3-PrO-4-MeOPh	3, 4-diMeOPh
2-96	3-ClPh	3-PrO-4-MeOPh	3-MeOPh
2-97	3-ClPh	3-PrO-4-MeOPh	4-MeOPh
2-98	3-MePh	3-PrO-4-MeOPh	3, 4-diMeOPh
2-99	3-MePh	3-PrO-4-MeOPh	3-MeOPh
2-100	3-MePh	3-PrO-4-MeOPh	4-MeOPh
2-101	3-TfmPh	3-MeO-4-PrOPh	3, 4-diMeOPh
2-102	3-TfmPh	3-MeO-4-PrOPh	3-MeOPh
2-103	3-TfmPh	3-MeO-4-PrOPh	4-MeOPh
2-104	3-TfmPh	3-PrO-4-MeOPh	3, 4-diMeOPh
2-105	3-TfmPh	3-PrO-4-MeOPh	3-MeOPh
2-106	3-TfmPh	3-PrO-4-MeOPh	4-MeOPh
2-107	3-TfmPh	3, 4-diPrOPh	3, 4-diMeOPh
2-108	3-TfmPh	3, 4-diPrOPh	3-MeOPh
2-109	3-TfmPh	3, 4-diPrOPh	4-MeOPh
2-110	3, 4-diMeOPh	Ph	3, 5-diMeO-4-PrSPh
2-111	3, 4-diMeOPh	Ph	4-MeSPh
2-112	3-MeO-4-PrOPh	Ph	3-MeS-4, 5-diMeOPh
2-113	3-MeO-4-PrOPh	3-MePh	3, 4, 5-triMePh
2-114	3-MeO-4-PrOPh	3-MePh	3, 4, 5-triEtPh
2-115	3-MeO-4-PrOPh	3-ClPh	3, 4-diEtPh
2-116	3-MeO-4-PrOPh	3-TfmPh	4-EtPh

Table 2 (continued)

Compound No.	R ¹	R ²	R ⁴
2-117	4-PrOPh	3, 4-diC ₆ H ₅	4-C ₆ H ₅
2-118	4-PrOPh	3-MePh	3, 4-diC ₆ H ₅
2-119	3-PrOPh	3-TfmPh	3-C ₆ H ₅
2-120	3-C ₆ H ₅	3-C ₆ H ₅	3-C ₆ H ₅ -4-MePh
2-121	3-MePh	3-MePh	3-Me-4-C ₆ H ₅
2-122	3-MePh	3-MePh	Ph
2-123	3-MeOPh	Ph	2-TfmPh
2-124	3-EtOPh	Ph	3-TfmPh
2-125	4-MeOPh	Ph	4-TfmPh
2-126	4-EtOPh	Ph	3, 4, 5-tri TfmPh
2-127	3, 4-diMeOPh	Ph	2-TfmPh
2-128	3, 4-diEtOPh	Ph	3-TfmPh
2-129	3-MeOPh	4-C ₆ H ₅	4-TfmPh
2-130	3-EtOPh	4-BrPh	3, 4, 5-tri TfmPh
2-131	4-MeOPh	4-FPh	2-TfmPh
2-132	4-EtOPh	4-C ₆ H ₅	3-TfmPh
2-133	3, 4-diMeOPh	4-FPh	4-TfmPh
2-134	3, 4-diEtOPh	4-BrPh	3, 4, 5-tri TfmPh
2-135	3-MeOPh	4-MePh	2-TfmPh
2-136	3-EtOPh	4-MePh	3-TfmPh
2-137	4-MeOPh	4-MePh	4-TfmPh
2-138	4-EtOPh	4-MePh	3, 4, 5-tri TfmPh
2-139	3, 4-diMeOPh	4-MePh	2-TfmPh
2-140	3, 4-diEtOPh	4-MePh	3-TfmPh
2-141	3-MeOPh	4-TfmPh	4-TfmPh
2-142	3-EtOPh	4-TfmPh	3, 4, 5-tri TfmPh
2-143	4-MeOPh	4-TfmPh	2-TfmPh
2-144	4-EtOPh	4-TfmPh	3-TfmPh
2-145	3, 4-diMeOPh	4-TfmPh	4-TfmPh

Table 2 (continued)

5	Compound No.	R ¹	R ²	R ⁴
10	2-146	3, 4-diEtOPh	4-TfmPh	3, 4, 5-triTfmPh
	2-147	3-MeOPh	3, 4-diClPh	2-TfmPh
	2-148	3-EtOPh	3, 4-diFPh	3-TfmPh
15	2-149	4-MeOPh	3, 4-diFPh	4-TfmPh
	2-150	4-EtOPh	3, 4-diClPh	3, 4, 5-triTfmPh
	2-151	3, 4-diMeOPh	3, 4-diClPh	2-TfmPh
	2-152	3, 4-diEtOPh	3, 4-diFPh	3-TfmPh
20	2-153	3-MeOPh	Ph	2-EtOPh
	2-154	3-EtOPh	Ph	3-EtOPh
	2-155	4-MeOPh	Ph	4-EtOPh
25	2-156	4-EtOPh	Ph	2, 3, 4-triEtOPh
	2-157	3, 4-diMeOPh	Ph	2-HOPh
	2-158	3, 4-diEtOPh	Ph	3-HOPh
30	2-159	3-MeOPh	4-ClPh	4-HOPh
	2-160	3-EtOPh	4-BrPh	3, 4, 5-triHOPh
	2-161	4-MeOPh	4-FPh	2-MeSPh
	2-162	4-EtOPh	4-ClPh	3-MeSPh
35	2-163	3, 4-diMeOPh	4-FPh	4-MeSPh
	2-164	3, 4-diEtOPh	4-BrPh	3, 4, 5-triMeSPh
	2-165	3-MeOPh	4-MePh	3, 4, 5-triEtSPh
40	2-166	3-EtOPh	4-MePh	2-EtOPh
	2-167	4-MeOPh	4-MePh	3-EtOPh
	2-168	4-EtOPh	4-MePh	4-EtOPh
45	2-169	3, 4-diMeOPh	4-MePh	2, 3, 4-triEtOPh
	2-170	3, 4-diEtOPh	4-MePh	2-HOPh
	2-171	3-MeOPh	4-TfmPh	3-HOPh
	2-172	3-EtOPh	4-TfmPh	4-HOPh
50	2-173	4-MeOPh	4-TfmPh	3, 4, 5-triHOPh
	2-174	4-EtOPh	4-TfmPh	2-MeSPh

55

Tabl 2 (continued)

Compound No.	R ¹	R ²	R ⁴
2-175	3,4-diMeOPh	4-TfmPh	3-MeSPh
2-176	3,4-diEtOPh	4-TfmPh	4-MeSPh
2-177	3-MeOPh	3,4-diClPh	3,4,5-triMeSPh
2-178	3-EtOPh	3,4-diFPh	3,4,5-triEtSPh
2-179	4-MeOPh	3,4-diFPh	2-EtOPh
2-180	4-EtOPh	3,4-diClPh	3-EtOPh
2-181	3,4-diMeOPh	3,4-diClPh	4-EtOPh
2-182	3,4-diEtOPh	3,4-diFPh	3,4,5-triEtOPh
2-183	3-MeOPh	Ph	2-ClPh
2-184	3-EtOPh	Ph	3-ClPh
2-185	4-MeOPh	Ph	4-ClPh
2-186	4-EtOPh	Ph	3,4,5-triClPh
2-187	3,4-diMeOPh	Ph	2-FPh
2-188	3,4-diEtOPh	Ph	3-FPh
2-189	3-MeOPh	4-ClPh	4-FPh
2-190	3-EtOPh	4-BrPh	3,4,5-triFPh
2-191	4-MeOPh	4-FPh	2-BrPh
2-192	4-EtOPh	4-ClPh	3-BrPh
2-193	3,4-diMeOPh	4-FPh	4-BrPh
2-194	3,4-diEtOPh	4-BrPh	3,4,5-triBrPh
2-195	3-MeOPh	4-MePh	2-ClPh
2-196	3-EtOPh	4-MePh	3-ClPh
2-197	4-MeOPh	4-MePh	4-ClPh
2-198	4-EtOPh	4-MePh	3,4,5-triClPh
2-199	3,4-diMeOPh	4-MePh	2-FPh
2-200	3,4-diEtOPh	4-MePh	3-FPh
2-201	3-MeOPh	4-TfmPh	4-FPh
2-202	3-EtOPh	4-TfmPh	3,4,5-triFPh
2-203	4-MeOPh	4-TfmPh	2-BrPh

Table 2 (continued)

Compound No.	R ¹	R ²	R ⁴
2-204	4-EtOPh	4-TfmPh	3-BrPh
2-205	3,4-diMeOPh	4-TfmPh	4-BrPh
2-206	3,4-diEtOPh	4-TfmPh	3,4,5-triBrPh
2-207	3-MeOPh	3,4-diClPh	2-ClPh
2-208	3-EtOPh	3,4-diFPh	3-ClPh
2-209	4-MeOPh	3,4-diFPh	4-ClPh
2-210	4-EtOPh	3,4-diClPh	3,4,5-triClPh
2-211	3,4-diMeOPh	3,4-diClPh	2-FPh
2-212	3,4-diEtOPh	3,4-diFPh	3-FPh

Table 3

Compound No.	R ¹	R ²	R ⁴
3-1	Ph	3, 4-diMeOPh	3, 4, 5-triMeOPh
3-2	3-ClPh	3, 4-diMeOPh	3, 4, 5-triMeOPh
3-3	3-TfmPh	3, 4-diMeOPh	3, 4, 5-triMeOPh
3-4	3-MePh	3, 4-diMeOPh	3, 4, 5-triMeOPh
3-5	4-MeOPh	3, 4-diClPh	3, 4, 5-triMeOPh
3-6	4-MeOPh	3, 4-diMePh	3, 4, 5-triMeOPh
3-7	3-ClPh	3-ClPh	3, 4, 5-triMeOPh
3-8	3-MePh	3-MePh	3, 4, 5-triMeOPh
3-9	3-ClPh	3-PrOPh	3, 4, 5-triMeOPh
3-10	3-ClPh	4-iBuOPh	3, 4, 5-triMeOPh
3-11	3-MePh	4-PrOPh	3, 4, 5-triMeOPh
3-12	3-MePh	4-iBuOPh	3, 4, 5-triMeOPh
3-13	3, 4-diClPh	4-PrOPh	3, 4, 5-triMeOPh
3-14	3, 4-diClPh	4-iBuOPh	3, 4, 5-triMeOPh
3-15	3, 4-diClPh	4-MePh	3, 4, 5-triMeOPh
3-16	3, 4-diClPh	4-iBuOPh	3, 4, 5-triMeOPh
3-17	Ph	3, 4-diMeOPh	3, 4-diMeOPh
3-18	3-ClPh	3, 4-diMeOPh	3, 4-diMeOPh
3-19	3-TfmPh	3, 4-diMeOPh	3, 4-diMeOPh
3-20	3-MePh	3, 4-diMeOPh	3, 4-diMeOPh
3-21	4-MeOPh	3, 4-diClPh	3, 4-diMeOPh
3-22	3-MeOPh	3, 4-diMePh	3, 4-diMeOPh
3-23	3-ClPh	3-ClPh	3, 4-diMeOPh
3-24	3-MePh	3-MePh	3, 4-diMeOPh
3-25	3-ClPh	4-PrOPh	3, 4-diMeOPh
3-26	3-ClPh	4-iBuOPh	3, 4-diMeOPh
3-27	3-MePh	4-PrOPh	3, 4-diMeOPh
3-28	3-MePh	4-iBuOPh	3, 4-diMeOPh
3-29	3, 4-diClPh	4-PrOPh	3, 4-diMeOPh

Table 3 (continued)

	Compound No.	R ¹	R ²	R ⁴
10	3-30	3, 4-diC ₁ Ph	4- <u>i</u> BuOPh	3, 4-diMeOPh
	3-31	3, 4-diC ₁ Ph	4-MePh	3, 4-diMeOPh
	3-32	3, 4-diC ₁ Ph	4- <u>i</u> BuOPh	3, 4-diMeOPh
15	3-33	Ph	3, 4-diMeOPh	4-MeOPh
	3-34	3-C ₁ Ph	3, 4-diMeOPh	4-MeOPh
	3-35	3-TfmPh	3, 4-diMeOPh	4-MeOPh
	3-36	3-MePh	3, 4-diMeOPh	4-MeOPh
20	3-37	4-MeOPh	3, 4-diC ₁ Ph	4-MeOPh
	3-38	4-MeOPh	3, 4-diMePh	4-MeOPh
	3-39	3-C ₁ Ph	3-C ₁ Ph	4-MeOPh
25	3-40	3-MePh	3-MePh	4-MeOPh
	3-41	3-C ₁ Ph	4-PrOPh	4-MeOPh
	3-42	3-C ₁ Ph	4- <u>i</u> BuOPh	4-MeOPh
30	3-43	3-MePh	4-PrOPh	4-MeOPh
	3-44	3-MePh	4- <u>i</u> BuOPh	4-MeOPh
	3-45	3, 4-diC ₁ Ph	4-PrOPh	4-MeOPh
	3-46	3, 4-diC ₁ Ph	4- <u>i</u> BuOPh	4-MeOPh
35	3-47	3, 4-diC ₁ Ph	4-MePh	4-MeOPh
	3-48	3, 4-diC ₁ Ph	4- <u>i</u> BuOPh	4-MeOPh
	3-49	Ph	3-MeO-4-PrOPh	3, 4, 5-triMeOPh
40	3-50	Ph	3, 4-diPrOPh	3, 4, 5-triMeOPh
	3-51	Ph	3-PrO-4-MeOPh	3, 4, 5-triMeOPh
	3-52	3-C ₁ Ph	3-MeO-4-PrOPh	3, 4, 5-triMeOPh
45	3-53	3-C ₁ Ph	3-PrO-4-MeOPh	3, 4, 5-triMeOPh
	3-54	3-C ₁ Ph	3, 4-diPrOPh	3, 4, 5-triMeOPh
	3-55	3-C ₁ Ph	3-MeOPh	3, 4, 5-triMeOPh
	3-56	3-MePh	3-MeO-4-PrOPh	3, 4, 5-triMeOPh
50	3-57	3-MePh	3-PrO-4-MeOPh	3, 4, 5-triMeOPh
	3-58	3-M Ph	3, 4-diPrOPh	3, 4, 5-triMeOPh

Table 3 (continued)

5	Compound No.	R ¹	R ²	R ⁴
10	3-59	3-TfmPh	3-MeO-4-PrOPh	3, 4, 5-triMeOPh
	3-60	3-TfmPh	3-PrO-4-MeOPh	3, 4, 5-triMeOPh
	3-61	3-TfmPh	3, 4-diPrOPh	3, 4, 5-triMeOPh
15	3-62	3-BrPh	3-MeO-4-PrOPh	3, 4, 5-triMeOPh
	3-63	3-BrPh	3-PrO-4-MeOPh	3, 4, 5-triMeOPh
	3-64	3-BrPh	3, 4-diPrOPh	3, 4, 5-triMeOPh
	3-65	3-BrPh	3-MeOPh	3, 4, 5-triMeOPh
20	3-66	3-BrPh	3-PrOPh	3, 4, 5-triMeOPh
	3-67	3-BrPh	4-MeOPh	3, 4, 5-triMeOPh
	3-68	3-BrPh	4-EtOPh	3, 4, 5-triMeOPh
25	3-69	3-BrPh	4-PrOPh	3, 4, 5-triMeOPh
	3-70	3-BrPh	4-BuOPh	3, 4, 5-triMeOPh
	3-71	3-TfmPh	3-MeOPh	3, 4, 5-triMeOPh
30	3-72	3-TfmPh	4-MeOPh	3, 4, 5-triMeOPh
	3-73	3-TfmPh	3-PrOPh	3, 4, 5-triMeOPh
	3-74	3-TfmPh	4-PrOPh	3, 4, 5-triMeOPh
	3-75	3-FPh	3-MeOPh	3, 4, 5-triMeOPh
35	3-76	3-FPh	4-MeOPh	3, 4, 5-triMeOPh
	3-77	3-FPh	3-PrOPh	3, 4, 5-triMeOPh
	3-78	3-FPh	4-PrOPh	3, 4, 5-triMeOPh
40	3-79	3, 5-diClPh	3-MeOPh	3, 4, 5-triMeOPh
	3-80	3, 5-diClPh	4-MeOPh	3, 4, 5-triMeOPh
	3-81	3, 5-diClPh	3-PrOPh	3, 4, 5-triMeOPh
45	3-82	3, 5-diClPh	4-PrOPh	3, 4, 5-triMeOPh

Of the compounds listed above, the preferred compounds are Compounds Nos. 1-1, 1-2, 1-3, 1-4, 1-6, 1-14, 1-16, 1-17, 1-18, 1-19, 1-20, 1-25, 1-26, 1-28, 1-29, 1-30, 1-41, 1-45, 1-46, 1-53, 1-76, 1-83, 1-91, 1-116, 1-117, 1-118, 1-120, 1-129, 1-130, 1-133, 1-134, 1-141, 1-154, 1-155, 1-207, 1-220, 1-298, 1-300, 1-313, 1-325, 1-327, 1-342, 1-343, 1-388, 1-411, 1-412, 1-419, 1-420, 1-424, 1-425, 1-426, 1-431, 1-433, 1-441, 1-445, 1-452, 1-453, 1-454, 1-455, 1-456, 1-457, 1-458, 1-459, 1-460, 1-461, 1-462, 1-463, 1-466, 1-467, 1-468, 1-469, 1-470, 1-471, 1-472, 1-473, 1-474, 1-475, 1-476, 1-477, 1-478, 1-479, 1-480, 1-481, 1-482, 1-483, 1-484, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-496, 1-498, 1-501, 1-505, 1-507, 1-510, 1-511, 1-512, 1-513, 1-514, 1-515, 1-516, 1-517, 1-518, 1-519, 1-520, 1-521, 1-522, 1-523, 1-524, 1-525, 1-528, 1-529, 1-530, 1-531, 1-536, 1-537, 1-539, 1-541, 1-546, 1-551, 1-552, 1-553, 1-556, 1-557, 1-558, 1-559, 1-560, 1-561, 1-562, 1-563, 1-564, 1-565, 1-566, 1-567, 1-568, 1-569, 1-570, 1-571, 1-

572, 1-573, 1-574, 1-580, 1-581, 1-582, 1-583, 1-584, 1-585, 1-586, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-593, 1-594, 1-595, 1-596, 1-598, 1-601, 1-602, 1-603, 1-604, 1-605, 1-606, 1-607, 1-608, 1-609, 1-610, 1-611, 1-612, 1-616, 1-621, 1-622, 1-623, 1-624, 1-625, 1-626, 1-627, 1-628, 1-629, 1-630, 1-631, 1-632, 1-633, 1-634, 1-635, 1-636, 1-637, 1-638, 1-639, 1-640, 1-641, 1-642, 1-643, 1-644, 1-645, 1-646, 1-647, 1-649, 1-650, 1-651, 1-652, 1-655, 1-659, 1-660, 1-661, 1-662, 1-663, 1-664, 1-665, 1-666, 1-667, 1-668, 1-669, 1-670, 1-671, 1-672, 1-673, 1-674, 1-675, 1-676, 1-677, 1-678, 1-679, 1-680, 1-681, 1-682, 1-683, 1-684, 1-685, 1-686, 1-687, 1-688, 1-689, 1-690, 1-691, 1-692, 1-693, 1-694, 1-695, 1-696, 1-697, 1-698, 1-699, 1-700, 1-701, 1-702, 1-703, 1-704, 1-705, 1-706, 1-707, 1-708, 1-709, 1-710, 1-711, 1-712, 1-713, 1-714, 1-715, 1-716, 1-717, 1-718, 1-719, 1-720, 1-721, 1-722, 1-723, 1-724, 1-725, 1-726, 1-727, 1-728, 1-729, 1-730, 1-731, 1-732, 1-733, 1-734, 1-735, 1-736, 1-737, 1-738, 1-739, 1-740, 1-741, 1-742, 1-743, 1-744, 1-745, 1-746, 1-747, 1-748, 1-749, 1-750, 1-751, 1-752, 1-753, 1-754, 1-755, 1-756, 1-757, 1-758, 1-759, 1-760, 1-761, 1-762, 1-763, 1-764, 1-766, 1-771, 1-772, 1-773, 1-774, 1-777, 1-778, 1-779, 1-780, 1-781, 1-782, 1-783, 1-784, 1-785, 1-787, 1-788, 1-789, 1-790, 2-1, 2-7, 2-8, 2-9, 2-15, 2-16, 2-19, 2-21, 2-23, 2-24, 2-25, 2-29, 2-30, 2-31, 2-32, 2-35, 2-37, 2-41, 2-44, 2-45, 2-46, 2-47, 2-51, 2-53, 2-57, 2-59, 2-62, 2-65, 2-66, 2-67, 2-68, 2-70, 2-72, 2-74, 2-75, 2-77, 2-78, 2-80, 2-83, 2-84, 2-85, 2-86, 2-87, 2-88, 2-89, 2-90, 2-91, 2-92, 2-93, 2-94, 2-101, 2-102, 2-103, 2-104, 2-107, 2-108, 2-109, 2-110, 2-112, 2-163, 3-1, 3-2, 3-3, 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-11, 3-13, 3-18, 3-19, 3-23, 3-25, 3-29, 3-34, 3-35, 3-37, 3-49, 3-50, 3-51, 3-52, 3-54, 3-56, 3-58, 3-59, 3-61, 3-62, 3-64, 3-67 and 3-68.

The more preferred compounds are Compounds Nos. 1-28, 1-53, 1-419, 1-424, 1-426, 1-431, 1-441, 1-445, 1-453, 1-454, 1-455, 1-456, 1-461, 1-462, 1-463, 1-464, 1-467, 1-468, 1-469, 1-470, 1-472, 1-475, 1-476, 1-478, 1-480, 1-482, 1-483, 1-484, 1-486, 1-510, 1-512, 1-513, 1-514, 1-515, 1-517, 1-519, 1-521, 1-524, 1-529, 1-531, 1-541, 1-546, 1-558, 1-560, 1-568, 1-570, 1-574, 1-581, 1-582, 1-585, 1-587, 1-590, 1-592, 1-594, 1-598, 1-603, 1-606, 1-609, 1-622, 1-627, 1-628, 1-631, 1-632, 1-637, 1-660, 1-668, 1-670, 1-671, 1-675, 1-679, 1-680, 1-681, 1-684, 1-685, 1-693, 1-694, 1-702, 1-703, 1-707, 1-710, 1-713, 1-714, 1-717, 1-718, 1-719, 1-727, 1-728, 1-730, 1-731, 1-733, 1-737, 1-740, 1-743, 1-746, 1-752, 1-758, 1-759, 1-772, 1-773, 1-777, 1-778, 1-784, 3-2, 3-3, 3-5, 3-49, 3-50, 3-52, 3-54, 3-56 and 3-59.

The most preferred compounds are:

1-28. 1-[3-(3,4-Dimethoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-419. 1-[3,3-Bis(3-chlorophenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-424. 1-[3,3-Bis(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-426. 1-[3,3-Bis(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-453. 1-[3-(2-Chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-454. 1-[3-(2-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-455. 1-[3-(2-Chlorophenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-467. 1-[3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-468. 1-[3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-469. 1-[3-(3-Chlorophenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-470. 1-[3-(3-Chlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-482. 1-[3-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-483. 1-[3-(3-Chlorophenyl)-3-(4-methoxy-3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-484. 1-[3-(3-Chlorophenyl)-3-(3,4-dipropoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-513. 1-[3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-515. 1-[3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-557. 1-[3-(3-Trifluoromethylphenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-559. 1-[3-(3-Trifluoromethylphenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-574. 1-[3-(3-Trifluoromethylphenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-590. 1-[3-(3-Methylphenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-594. 1-[3-(3-Methylphenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-603. 1-[3-(3-Methoxy-4-propoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-606. 1-[3-(3,4-Dipropoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-622. 1-[3-(4-Ethoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-627. 1-[3-(4-Butoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
 1-685. 1-[3-(3-Methoxy-4-propoxyphenyl)-3-(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;

1-710. 1-[3-(3-Methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine;

1-740. 1-[3-(3-Chlorophenyl)-3-(3-methoxy-4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine; and

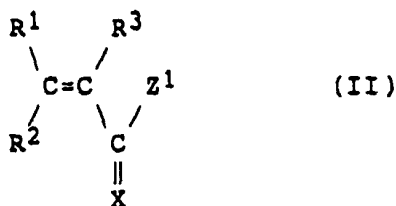
5 1-743. 1-[3-(3-Chlorophenyl)-3-(4-ethoxy-3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine.

The N-acryloylpiperazine and N-acryloylhomopiperazine derivatives of the present invention can be prepared by the procedures described below.

Where it is desired to prepare any compound of the present invention which has a thiocarbonyl group in its molecule, it can, in general, be prepared by any of the reactions described below from the corresponding starting material also having a thiocarbonyl group in its molecule. Alternatively, such compounds can also be prepared by first synthesizing the corresponding compound having a carbonyl group in its molecule and then reacting the carbonyl compound with a reagent which converts the carbonyl group into a thiocarbonyl group, such as Lawesson's Reagent [which consists mainly of [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide] by conventional means. If the compound has two carbonyl groups in its molecule, selective conversion of these two carbonyl groups into either two thiocarbonyl groups or one thiocarbonyl group is possible by selection of the reaction conditions.

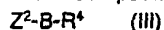
In general terms, the compounds of the present invention may be prepared by reacting a compound of formula (II):

20



25

30 with a compound of formula (III):



(in which one of Z¹, in formula (I), and Z², in formula (II), represents a group represented by Y and the other of Z¹ and Z² represents a group of formula -A-H; Y represents a nucleophilic leaving group; and R¹, R², R³, R⁴, X, A and B are as defined above).

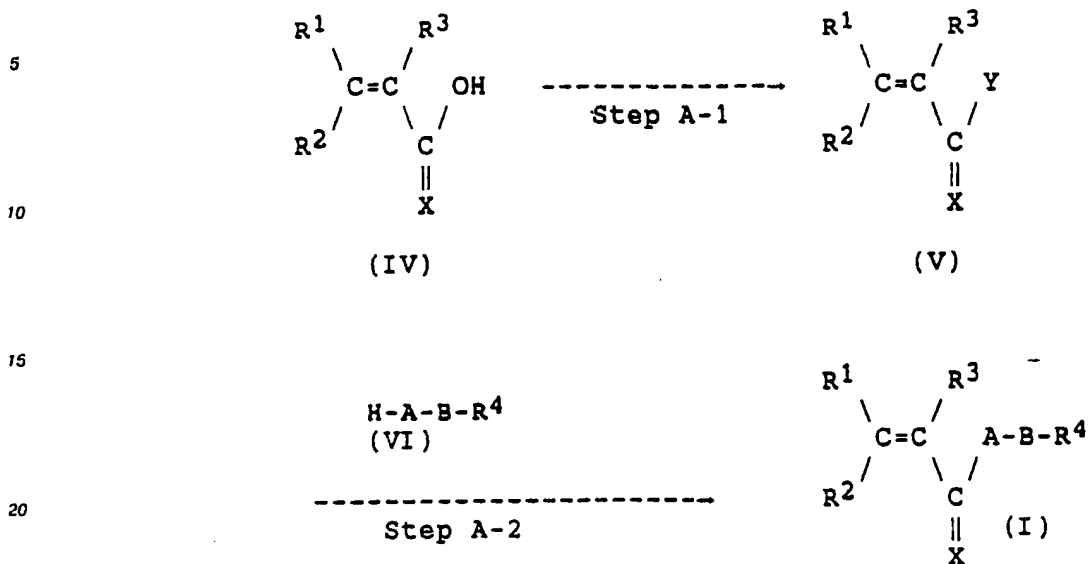
35 Examples of nucleophilic leaving groups which may be represented by Y include: halogen atoms, such as the chlorine, bromine or iodine atoms; azide groups; and lower alkoxy carbonyloxy groups in which the alkoxy part has from 1 to 4, preferably 1 or 2, carbon atoms, such as the methoxycarbonyloxy and ethoxycarbonyloxy groups.

40 More specifically, examples of preferred methods of preparing the compounds of the present invention are as illustrated in the following Methods A and B.

45

50

55

Method A:

In these formulae, R¹, R², R³, R⁴, X, A, B and Y are as defined above.

In Step A-1, the carboxylic acid derivative of formula (IV) is converted to an activated derivative thereof of formula (V).

This activation may be carried out using conventional techniques, which will, of course, depend on the nature of the active derivative of formula (V) to be prepared. For example, where it is desired to prepare an acyl halide compound, a phosphorus chloride (such as phosphorus pentachloride or phosphorus trichloride) or a sulphuric acid derivative (such as thionyl chloride) is reacted with the carboxylic acid of formula (IV). Where it is desired to prepare an acyl azide compound, an azidation reagent, such as diphenylphosphorylazide (DPPA), is employed, together with an organic base. Where it is desired to prepare a lower alkoxycarbonyloxy compound, a lower alkyl halocarboxylate, such as ethyl chloroformate, is employed, together with an organic base.

Where an organic base is employed in this reaction, there is no particular limitation on its nature, and any base commonly used for this type of reaction may equally be employed here. Examples of suitable organic bases include: trialkylamines, such as triethylamine and diisopropylethylamine; and cyclic amines, such as N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, N,N-dimethylaniline, 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-diazabicyclo[2.2.2]octane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

In Step A-2, the compound of formula (I) of the present invention is prepared by reacting the activated carboxylic acid derivative of formula (V) with the compound of formula (VI). This reaction may take place in the presence or absence of a base and preferably in a solvent.

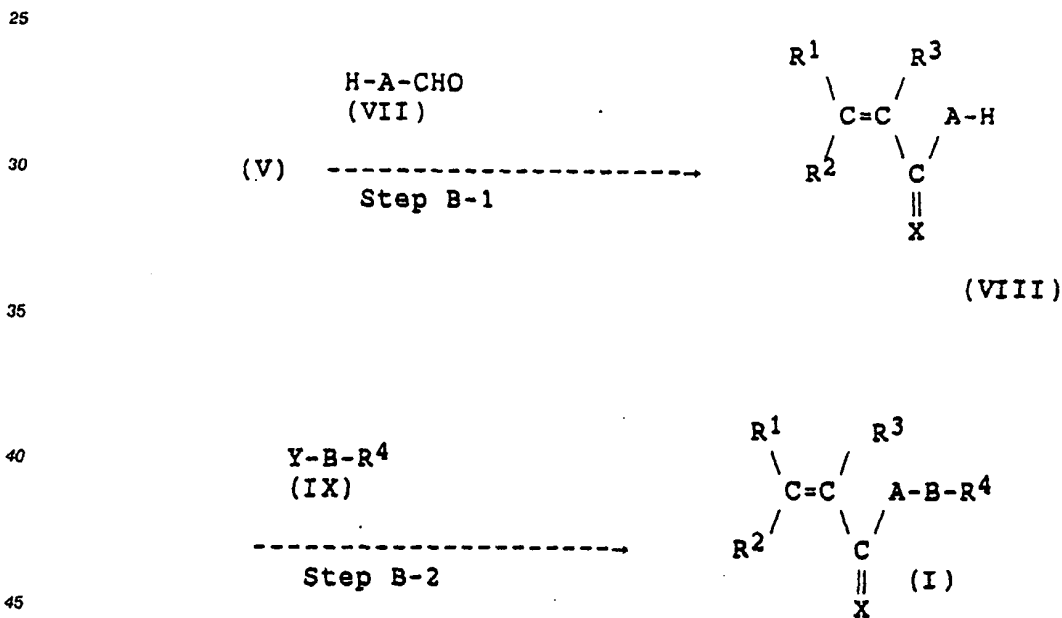
When the activated carboxylic acid derivative of formula (V) is an acyl halide, a base is preferably employed. There is no particular restriction on the nature of the base employed for this reaction, and any base commonly employed in reactions of this type may equally be employed here. If an inorganic base [for example: an alkali metal carbonate (such as sodium carbonate or potassium carbonate); an alkali metal bicarbonate (such as sodium bicarbonate or potassium bicarbonate); an alkali metal hydride (such as lithium hydride, sodium hydride or potassium hydride); or an alkali metal hydroxide (such as sodium hydroxide, potassium hydroxide or barium hydroxide)] is employed, the preferred solvent is: an ether, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; an amide, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; a sulfoxide such as dimethyl sulfoxide; a nitrile such as acetonitrile; water; or a mixture of water with any one or more of the organic solvents mentioned above. If an organic base [such as triethylamine, diisopropylethylamine, N-methylmorpholine, pyridine, 4-(N,N-dimethylamino)pyridine, N,N-dimethylaniline, 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-diazabicyclo[2.2.2]octane or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)] is employed, the preferred solvent is: an aromatic hydrocarbon, such as benzene, toluene or xylene; an ether, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; or a halogenated hydrocarbon, especially a halogenated aliphatic hydrocarbon, such as methylene chloride or chloroform.

When the activated carboxylic acid derivative of formula (V) is an acyl azide compound or a lower alkoxycarbonyloxy compound, the organic base mentioned above is not always necessary, because the reaction will proceed even in the absence of the base. However, a base may be employed, if desired. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride or chloroform; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; sulfoxides, such as dimethyl sulfoxide; and nitriles, such as acetonitrile.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature from 0°C to 50°C, preferably at room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 15 minutes to 1 day will usually suffice.

Certain of the compounds of formula (VI) used in Step A-2 are known {for example, 1-(3,4,5-trimethoxybenzoyl)piperazine, L. Toldy et al., *Acta. Chim. Acad. Sci. Hung.*, 49 (3), 265 - 285 (1966), and 1-[3,4,5-trimethoxy(thiobenzoyl)]piperazine, C. Farina et al., *Eur. Med. Chem. Chimica Therapeutica*, 14 (1), 27 - 31 (1979)}. Otherwise, they can be prepared by the reaction of the compound of formula (VII) with the compound of formula (IX) both of which will be described later, according to Method B.

Method B:



In these formulae, R¹, R², R³, R⁴, Y, X, A and B are as defined above.

In Step B-1, a compound of formula (VIII) is prepared by: first, reacting the activated carboxylic acid derivative of formula (V) (prepared as described in Step A-1) with the compound of formula (VII); and then removing the formyl group which is a substituent on the nitrogen atom of the piperazine or homopiperazine ring "A". The reaction in the first part of this Step is essentially the same as and may be carried out under the same conditions as that of Step A-2, and using the same reagents as described therein.

The removal of the formyl group in the latter half of the Step is carried out by treating the formyl compound prepared in the first part of the Step with a base in the presence of a solvent. There is no particular restriction on the nature of the base employed, provided that it does not affect any other part of the compounds in the reaction mixture. The reaction is preferably carried out using as the base: a metal alkoxide, such as sodium methoxide; an alkali metal carbonate, such as sodium carbonate or potassium

carbonate; an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide; aqueous ammonia or concentrated methanolic ammonia. There is no particular restriction on the nature of the solvent employed, provided that it has no adverse effect on the reagents and that it is capable of dissolving the reagents, at least to some extent. Examples of suitable solvents include any of those commonly used for hydrolytic reactions, for example, an organic solvent, such as: an alcohol, e.g. methanol, ethanol or propanol; or an ether, such as tetrahydrofuran or dioxane; also water or a mixture of water with any one or more of the organic solvents mentioned above may be used.

The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention. In general, in order to avoid side reactions, we find it convenient to carry out the reaction at a temperature in the range of from 0 °C to 150 °C, preferably at room temperature, although the exact preferred temperature may vary depending upon the starting materials, the base and the reaction solvent. The time required for the reaction may likewise vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, in most cases, a period of from 1 to 24 hours will normally suffice.

In Step B-2, a compound of formula (I) is prepared by reacting a compound of formula (VIII) with a compound of formula (IX) in the presence of a base and in a solvent.

Where B represents any group other than a lower alkylene group, the reaction is essentially the same as and may be carried out according to the procedure described in Step A-2. When B represents a lower alkylene group, the base is preferably an alkali metal hydride, such as lithium hydride, sodium hydride or potassium hydride. There is no particular restriction on the nature of the solvent employed, provided that it does not hinder the reaction and that it can dissolve the starting materials at least to some degree. Preferred solvents are: ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; and amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide.

After completion of the reaction, the desired compound from every reaction mentioned above can be collected from the reaction mixture by conventional means. For example, it can be obtained by adding a water-immiscible organic solvent to the reaction mixture, followed by washing with water, and then distilling off the solvent. The compound thus obtained can, if necessary, be further purified by conventional means, such as recrystallization, reprecipitation or the various chromatography techniques, notably column chromatography.

The carboxylic acid derivative of formula (IV), in which X represents an oxygen atom, that is to say the compound of formula (XIII), which is one of the starting materials employed in the process of the present invention may be prepared as illustrated in the following Method C:

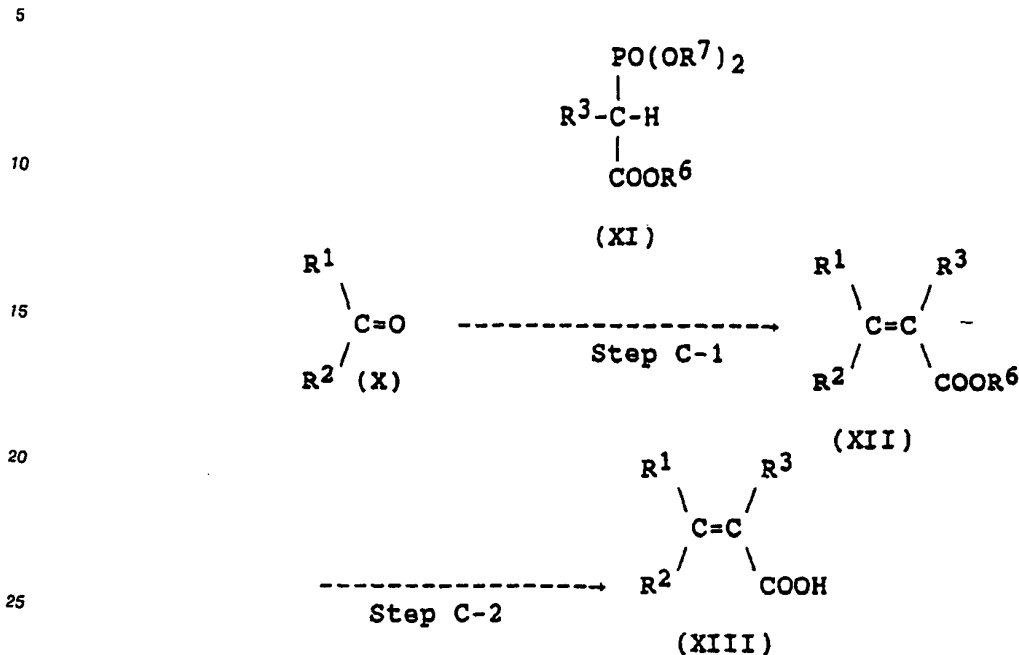
35

40

45

50

55

Method C:

30 In these formulae, R¹, R² and R³ are as defined above, R⁶ represents a C₁ - C₆ alkyl group, and R⁷ represents a C₁ - C₆ alkyl group or an aryl group which may optionally be substituted, as defined above in relation to R⁵.

In Step C-1, a compound of formula (XII) is prepared by reacting a ketone compound of formula (X) with Horner's reagent, the compound of formula (XI). This reagent can be prepared, for example, by the well known Arbuzov reaction. Step C-1 takes place in the presence of a base and in a solvent.

35 There is no particular restriction on the nature of the base employed, provided that it has no adverse effect on other parts of the molecule. Examples of suitable bases include: inorganic bases, such as alkali metal hydrides (e.g. lithium hydride, sodium hydride or potassium hydride) and alkali metal hydroxides (e.g. sodium hydroxide, potassium hydroxide or barium hydroxide); organic bases, such as 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-diazabicyclo[2.2.2]octane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); and organic metal bases, such as butyllithium and lithium diisopropylamide.

40 There is no particular restriction on the nature of the solvent employed, provided that it does not hinder the reaction and that it can dissolve the starting materials, at least to some degree. Examples of preferred solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane; amides, such as dimethylformamide, dimethylacetamide or hexamethylphosphoric triamide; and sulfoxides, such as dimethyl sulfoxide.

45 In Step C-2, the starting material of formula (XIII) used in the present invention is prepared by removing the group R⁶, which is the carboxy-protecting group in the compound of formula (XII).

50 Removal of the protecting group may be carried out by any known reaction for removing groups of this type, for example by treatment with an acid or a base. Examples of suitable acids include hydrochloric acid, sulphuric acid, phosphoric acid and hydrobromic acid. There is no particular restriction on the nature of the base, provided that it does not affect other parts of the compounds in the reaction mixture; however, we prefer to use: an alkali metal carbonate, such as sodium carbonate or potassium carbonate; an alkali metal hydroxide, such as sodium hydroxide or potassium hydroxide; or concentrated methanolic ammonia. There is likewise no particular restriction on the nature of the solvent, and any solvent commonly used for hydrolytic reactions may equally be used here, provided that it has no adverse effect on any of the reagents and that it is capable of dissolving the reagents, at least to some extent. Examples include water, and mixtures of water with an organic solvent, for example: an alcohol such as methanol, ethanol or propanol; or an ether, such as tetrahydrofuran or dioxane.

The reaction will take place over a wide range of temperatures, and the precise reaction temperature chosen is not critical to the invention, although the preferred temperatures may vary depending on the starting materials and the base employed. In general, we find it convenient to carry out the reaction at a temperature in the range of from 0°C to 150°C. The time required for the reaction may likewise vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, in most cases, a period of from 1 to 10 hours will normally suffice.

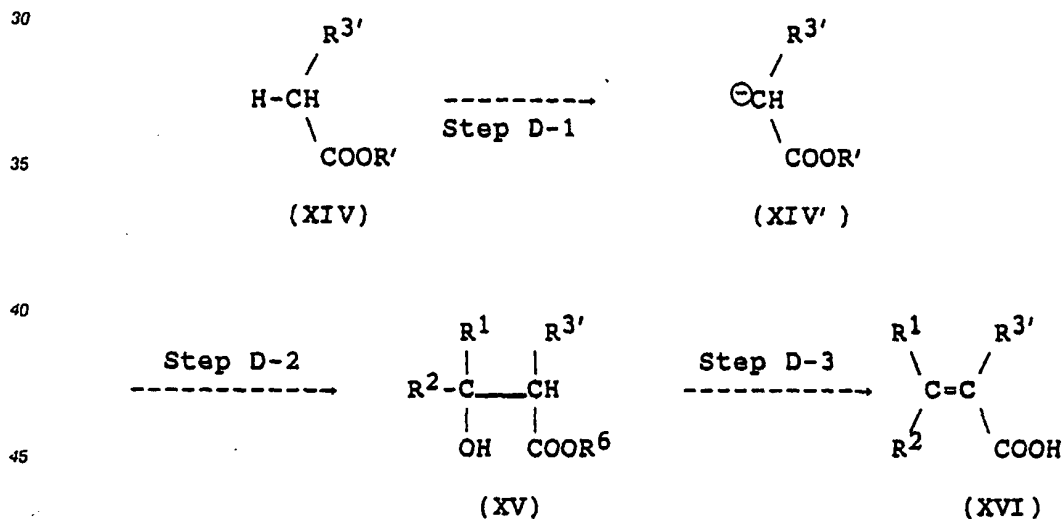
When the substituents R¹ and R² are different, the product will normally be obtained as a mixture of its geometrical isomers. By using chromatography or similar techniques, as is well known, in each of Steps C-1 and C-2, the (E)-form and (Z)-form can be obtained separately, if desired.

In general, the compounds of formula (X), which are starting materials in this reaction, are well known. However, where they are not, they can be prepared, for example, by reacting a compound of formula R¹-CHO (in which R¹ is as defined above) with a compound of formula R²-MgZ (in which R² is as defined above and Z represents a halogen atom) or with a compound of formula R²-Li (in which R² is as defined above), or by reacting a compound of formula R²-CHO (in which R² is as defined above) with a compound of formula R¹-MgZ (in which R¹ and Z are as defined above) or with a compound of formula R¹-Li (in which R¹ is as defined above), followed by oxidizing the alcohol compound thus formed to its corresponding carbonyl compound by conventional means.

Further, by application of the famous Friedel-Crafts reaction, these compounds of formula (X) can be also prepared by reacting a compound of formula R¹H (in which R¹ is as defined above) with a compound of formula R²-COZ (in which R² and Z are as defined above), or by reacting a compound of formula R²H (in which R² is as defined above) with a compound of formula R¹-COZ (in which R¹ and Z are as defined above).

The following Method D provides an alternative method of preparing a compound of formula (XIII), in which R³ does not represent a hydrogen atom, that is to say a compound of formula (XVI).

Method D:



In the above formulae, R¹, R² and R⁶ are as defined above; R³ represents any of the groups in the definition of R³ other than a hydrogen atom; and R' represents a carboxy-protecting group, which may or may not be the same as the group represented by R⁶.

In this reaction scheme, the starting material of formula (XVI) of the present invention is prepared by treating a compound of formula (XIV) with a base in the presence of solvent at -78°C - 0°C to yield an anion of formula (XIV') (Step D-1), which is then reacted, in Step D-2, with a compound of formula (X) (see Method C); this is then treated, in Step D-3, with a dehydrating agent, such as an acid or phosphorus oxychloride, in the presence or absence of a solvent, and then the ester group is hydrolyzed by conventional means.

In Steps D-1 and D-2, there is no particular restriction on the nature of the solvent to be employed.

provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; amides, such as formamide, dimethylformamide, dimethylacetamide and hexamethylphosphoric triamide; and sulphoxides, such as dimethyl sulphoxide and sulfolane.

There is no particular restriction on the nature of the base employed for the reaction of Step D-1, and any base commonly employed in reactions of this type may equally be employed here. Examples of suitable bases include: inorganic bases, such as alkali metal hydrides (e.g. lithium hydride, sodium hydride or potassium hydride); organic bases, such as 1,5-diazabicyclo[4.3.0]nona-5-ene, 1,4-diazabicyclo[2.2.2]octane or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); and organic metal bases such as butyllithium and lithium diisopropylamide.

In Step D-2, which is preferably carried out without intermediate isolation of the anion of formula (XIV') produced in Step D-1, the anion is reacted with a compound of formula (X), to give a compound of formula (XV). The reaction is preferably carried out in the same reaction medium and under the same conditions as Step D-1.

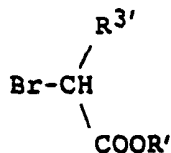
Step D-3 consists of the reaction of the resulting compound of formula (XV) with a dehydrating agent, to give the desired compound of formula (XVI). This reaction may take place in the presence or absence of a solvent. There is no particular restriction on the nature of the solvent, where it is employed, provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane and heptane; aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene and the dichlorobenzenes; esters, such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate and diethyl carbonate; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane and diethylene glycol dimethyl ether; alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerine, octanol, cyclohexanol and methylcellosolve (ethylene glycol monomethyl ether); ketones, such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone and cyclohexanone; nitro compounds, such as nitroethane and nitrobenzene; nitriles, such as acetonitrile and isobutyronitrile; amides, such as formamide, dimethylformamide, dimethylacetamide and hexamethylphosphoric triamide; and sulphoxides, such as dimethyl sulphoxide and sulfolane.

There is likewise no particular restriction on the nature of the acid employed for this reaction, and any acid commonly employed as a proton donor and classified as a Brønsted acid may equally be employed here. Examples of suitable acids include: organic acids, such as *p*-toluenesulphonic acid or camphorsulphonic acid; and inorganic acids, such as hydrochloric acid or sulphuric acid.

When an phosphorus oxychloride is employed as the dehydrating reagent, an aprotic solvent should be used. Preferred such solvents include the aliphatic hydrocarbons, aromatic hydrocarbons or halogenated hydrocarbons listed above.

When the substituents R¹ and R² are different, the product will normally be obtained as a mixture of its geometric isomers. By using chromatography or similar techniques, as is well known, the *Z*-form and the *E*-form can be obtained separately, if desired.

Alternatively, the starting material of formula (XVI) may be prepared by reacting the compound of formula (X) with a compound of formula:



using activated zinc powder in the presence of a solvent according to the same Reformatsky reaction as is reported by Kametani *et al.* [Yakugakuzassi, **88**, 911 (1968)], followed by dehydration and hydrolysis in a similar manner to that described above.

There is no particular restriction on the nature of the solvent to be employed in the Reformatsky reaction, provided that it has no adverse effect on the reaction or on the reagents involved. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane or heptane; and aromatic hydrocarbons, such as benzene, toluene or xylene, preferably aromatic hydrocarbons.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from 0°C to the boiling point of the reaction medium, preferably at a temperature from 80°C to 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature, the nature of the reagents, and the nature of the solvent. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 24 hours, preferably from 2 to 6 hours, will usually suffice.

An alternative method of preparing the compound of formula (XIII) in which R² represents a group -R⁵, as defined above, that is to say a compound of formula (XVIII), is shown in Method E:

Method E:



In these formulae, R¹, R³ and R⁶ are as defined above, and R² represents a group of formula -R⁵, as defined above for R².

In Step E-1, the compound of formula (XVIII) is prepared, by reacting the compound of formula (XVII), according to Heck's reaction, with a compound of formula R²-Y (in which R² and Y are as defined above) in the presence of a palladium salt, such as palladium acetate, in a solvent, after which the carboxy-protecting group, R⁶, may be removed, as mentioned above.

There is no particular restriction on the nature of the solvent employed, provided that it does not hinder the reaction and that it can dissolve the starting compounds, at least to some degree. Examples of preferred solvents include: nitriles, such as acetonitrile; aromatic hydrocarbons, such as benzene, toluene and xylene; esters, such as ethyl acetate and propyl acetate; ethers, such as diethyl ether, tetrahydrofuran, dioxane and dimethoxyethane; amides, such as dimethylformamide, dimethylacetamide and hexamethylphosphoric triamide; and sulphoxides, such as dimethyl sulphoxide.

The compound of formula (XVII) used as the starting material can be prepared from a compound of formula R¹-CHO (in which R¹ is as defined above), using the techniques of Method C or Method D.

An alternative method of preparing a compound of formula (XII) in which R³ represents a hydrogen atom, that is to say a compound of formula (XXI), is shown in Method F:



In these formulae, R¹, R², R⁶ and Z are as defined above.

In Step F-1, the compound of formula (XXI) is prepared from the compound of formula (XX).

When R² is R⁵ (as defined above), the compound of formula (XXI) is prepared by reacting the compound of formula (XX) with a compound of formula R²-MgZ (in which R² and Z are as defined above) in the presence of a divalent nickel complex such as bis(disphenylphosphino)ethane nickel (II) chloride in a

solvent, after which the carboxy-protecting group, R^6 , may be removed by the procedure mentioned above.

There is no particular restriction on the nature of the solvent employed, provided that it does not hinder the reaction and that it can dissolve the starting compounds, at least to some degree. Examples of preferred solvents include: aromatic hydrocarbons, such as benzene, toluene or xylene; and ethers, such as diethyl ether, tetrahydrofuran, dioxane or dimethoxyethane.

When R^2 represents any group other than R^2 , the compound of formula (XXI) may be prepared by reacting the compound of formula (XX) with a compound of formula $R^5-CH=CH_2$ (in which R^5 is as defined above) or with a compound of formula $R^5-C\equiv CH$ (in which R^5 is as defined above) in the presence of a palladium complex such as bis(triphenylphosphine) palladium (II) chloride in a solvent, after which the carboxy-protecting group, R^6 , may be removed, as described above.

In the first part of this reaction, the reaction may occasionally be carried out preferably in the presence of an organic base, such as triethylamine.

There is no particular restriction on the nature of the solvent employed in this reaction, provided that it does not hinder the reaction and that it can dissolve the compounds used as starting materials, at least to some degree. Examples of preferred solvents include: aromatic hydrocarbons, such as benzene, toluene and xylene; halogenated hydrocarbons, especially halogenated aliphatic hydrocarbons, such as methylene chloride and chloroform; ethers, such as diethyl ether, tetrahydrofuran, dioxane and dimethoxyethane; amides, such as dimethylformamide, dimethylacetamide and hexamethylphosphoric triamide; and sulphoxides, such as dimethyl sulphoxide.

The compound of formula (XX) used as the starting material in this reaction can be prepared by the addition of a halogen atom, such as a chlorine or bromine atom, to a compound of formula (XVII) in which R^3 represents a hydrogen atom, followed by removing a hydrogen halide, such as hydrogen bromide or hydrogen chloride, to form a triple bond, and then followed by the addition of a hydrogen halide such as hydrogen bromide.

As will be demonstrated hereafter, the novel N-acryloylpiperazine derivatives of the present invention have an excellent PAF-antagonist activity, and, moreover, have excellent stability on oral administration. Accordingly, these derivatives are expected to be useful for the therapy and prophylaxis of various diseases and disorders in which PAF is thought to be implicated, such as endotoxin-induced shock, anaphylactic shock, nephritis, myocardial infarction, angina pectoris, asthma, psoriasis and gastric ulceration.

The compounds of the invention may be administered orally or parenterally, as required, and may, if desired, be formulated into appropriate pharmaceutical preparations, the nature of which will depend upon the desired route of administration. For example, for oral administration, the compounds may be formulated as tablets, capsules, granules, powders or syrups. For parenteral administration, they may be formulated as injectible solutions or suspensions or as suppositories. Although the preferred dose will vary, depending upon the nature of the disorder, as well as upon the symptoms, age, condition and body weight of the patient and the route of administration, a preferred dose for an adult human patient would normally be expected to be from 0.2 to 50 mg/kg body weight per day, and this could be administered in a single dose or in divided doses.

These preparations can be formulated using any conventional additives such as vehicles, binders, disintegrating agents, lubricants, stabilizers and corrigents, as is well known in the art.

The invention is further illustrated by the following non-limiting Examples. Preparation of certain of the starting materials employed in these Examples is illustrated by the subsequent Preparations. The biological activities of certain of the compounds of the invention are then illustrated in the subsequent Experiments, and these are followed by examples of Formulations of the invention.

EXAMPLE 1

1-(3,3-Diphenylacryloyl)-4-(3,4,5-trimethoxybenzoyl)piperazine

4.164 g of phosphorus pentachloride were added to 90 ml of a methylene chloride solution containing 4.485 g of 3,3-diphenylacrylic acid, which had previously been cooled at 0 - 5 °C. The reaction mixture was then stirred for one hour at room temperature, after which the solvent was distilled off under reduced pressure. The resulting residue was dissolved in 50 ml of toluene, and then the solvent was once again distilled off under reduced pressure. This procedure comprising dissolution and distillation was repeated once more. 3,3-Diphenylacryloyl chloride was obtained as a white solid. This crude product was imme-

diately used in the next reaction.

0.840 g of sodium bicarbonate dissolved in 15 ml of water was added to 30 ml of a tetrahydrofuran solution containing 1.401 g of 1-(3,4,5-trimethoxybenzoyl)piperazine. 1.214 g of the 3,3-diphenylacryloyl chloride obtained as described above were added to the mixture, in one go, and the resulting mixture was stirred for 30 minutes at room temperature. At the end of this time, 50 ml of methylene chloride were added to the reaction mixture, the organic phase and the aqueous phase were separated from each other, and the aqueous phase was extracted with methylene chloride. The methylene chloride phase and the methylene chloride extract were combined and washed with 10% w/v aqueous hydrochloric acid, with a 5% w/v aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order. The methylene chloride solution was dried over anhydrous sodium sulphate, and then the solvent was removed by distillation under reduced pressure. The oily residue (2.70 g) was purified by silica gel flash chromatography. Those fractions which were eluted with a 100 : 1 by volume mixture of methylene chloride and methanol were collected to afford 2.150 g of the title compound as a white powder. Recrystallization of this from a mixture of ethyl acetate and hexane gave white needles, melting at 148 - 150 °C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.65 - 3.80 (8H, multiplet);

3.84 (6H, singlet);

3.85 (3H, singlet);

6.30 (1H, singlet);

6.52 (2H, singlet);

7.2 - 7.5 (10H, multiplet).

Mass spectrum (m/z):

486 (M⁺), 291 (M⁺ - C₁₀H₁₁O₄), 279 (M⁺ - CH₁₅H₁₁O), 207 (C₁₅H₁₁O), 195 (C₁₀H₁₁O₄).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1630, 1585.

Elemental analysis:	
Calculated for C ₂₉ H ₃₀ N ₂ O ₅ :	
Found:	C, 71.59%; H, 6.21%; N, 5.76%.
	C, 71.54%; H, 6.44%; N, 5.71%.

EXAMPLE 2

1-[3,3-Bis(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Following a procedure similar to that described in Example 1, but using 0.500 g of 3,3-bis(4-methoxyphenyl)acrylic acid, 0.362 g of the title compound was obtained as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.70 - 3.75 (8H, multiplet);

3.82 (3H, singlet);

3.84 (3H, singlet);

3.85 (9H, singlet);

6.14 (1H, singlet);

6.54 (2H, singlet);

6.80 - 6.93 (4H, multiplet);

7.18 - 7.30 (4H, multiplet).

Mass spectrum (m/z):

546 (M⁺), 351 (M⁺ - C₁₀H₁₁O₄), 279 (M⁺ - C₁₇H₁₅O₃), 267 (C₁₇H₁₅O₃), 195 (C₁₀H₁₁O₄).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1605, 1585.

EXAMPLE 35 1-[3,3-Bis(4-chlorophenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Following a procedure similar to that described in Example 1, but using 0.500 g of 3,3-bis(4-chlorophenyl)acrylic acid, 0.938 g of the title compound was obtained as a white powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

10 2.90 - 3.70 (8H, multiplet);

3.86 (9H, singlet);

6.32 (1H, singlet);

6.56 (2H, singlet);

7.15 - 7.40 (8H, multiplet).

15 Mass spectrum (m/z):

554 (M⁺), 359 (M⁺ - C₁₀H₁₁O₄), 279 (M⁺ - C₁₅H₉Cl₂O), 275 (C₁₅H₉Cl₂O); 195 (C₁₀H₁₁O₄).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1630, 1590.

20

EXAMPLE 425 1-[3,3-Bis(2-thienyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Following a procedure similar to that described in Example 1, but using 0.500 g of 3,3-bis(2-thienyl)acrylic acid, 0.719 g of the title compound was obtained as a white powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

30 2.90 - 3.75 (8H, multiplet);

3.85 (9H, singlet);

6.34 (1H, singlet);

6.57 (2H, singlet);

7.02 (1H, doublet of doublets, J = 5.13 & 3.66 Hz);

35 7.08 (1H, doublet of doublets, J = 5.13 & 3.66 Hz);

7.13 (1H, doublet of doublets, J = 1.10 & 3.66 Hz);

7.26 (1H, doublet of doublets, J = 1.10 & 3.66 Hz);

7.32 (1H, doublet of doublets, J = 5.13 & 1.10 Hz);

7.42 (1H, doublet of doublets, J = 5.13 & 1.10 Hz).

40 Mass spectrum (m/z):

498 (M⁺), 303 (M⁺ - C₁₀H₁₁O₄), 279 (M⁺ - C₁₁H₇OS₂), 219 (C₁₁H₇OS₂), 195 (C₁₀H₁₁O₄).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1620, 1585.

45

Elemental analysis:	
Calculated for C ₂₅ H ₂₆ N ₂ O ₅ S ₂ :	
Found:	C, 60.22%; H, 5.26%; N, 5.62%; S, 12.86%.
	C, 60.34%; H, 5.43%; N, 5.59%; S, 12.97%.

50

55

EXAMPLE 5

1-[(Z)-3-Phenyl-3-(2-thienyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Following a procedure similar to that described in Example 1, but using 0.480 g of (Z)-3-phenyl-3-(2-thienyl)acrylic acid (prepared as described in Preparation 1, Isomer A, melting at 144 - 147°C), 0.703 g of the title compound was obtained as a white powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.70 - 3.75 (8H, multiplet);

3.84 (3H, singlet);

3.85 (6H, singlet);

6.41 (1H, singlet);

6.53 (2H, singlet);

6.88 (1H, doublet of doublets, J = 3.67 & 1.10 Hz);

6.98 (1H, doublet of doublets, J = 5.13 & 3.67 Hz);

7.30 (1H, doublet of doublets, J = 5.13 & 1.10 Hz);

7.40 (5H, singlet-like).

Mass spectrum (m/z):

492 (M⁺), 297 (M⁺ - C₁₀H₁₁O₄), 279 (M⁺ - C₁₃H₉OS), 213 (C₁₃H₉OS), 195 (C₁₀H₁₁O₄).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1620, 1585.

Elemental analysis:

Calculated for C₂₇H₂₈N₂O₅S:

Found:	C, 65.83%; H, 5.73%; N, 5.69%; S, 6.51%.
	C, 65.68%; H, 5.97%; N, 5.79%; S, 6.51%.

EXAMPLE 61-[(E)-3-Phenyl-3-(4-pyridyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

1 ml of a methylene chloride solution containing 0.330 g of diphenylphosphoryl azide and then 0.280 g of 1-(3,4,5-trimethoxybenzoyl)piperazine were added to 5 ml of a methylene chloride solution containing both 0.224 g of (E)-3-phenyl-3-(4-pyridyl)acrylic acid (prepared as described in Preparation 3) and 0.28 ml of triethylamine. The mixture was then stirred for 4 hours at room temperature, after which the reaction solution was diluted with 20 ml of methylene chloride. It was then washed with a 5% w/v aqueous solution of sodium bicarbonate, followed by a saturated aqueous solution of sodium chloride, and the organic phase was dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the oily residue (0.686 g) was purified by silica gel flash chromatography. 0.419 g of the title compound was obtained as a white powder from the fractions eluted with mixtures of methylene chloride and methanol ranging from 100 : 2 to 100 : 3 by volume.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

3.05 - 3.70 (8H, multiplet);

3.84 (9H, multiplet);

6.50 (1H, singlet);

6.58 (2H, singlet);

7.10 - 7.68 (7H, multiplet);

8.45 - 8.85 (2H, multiplet).

Mass spectrum (m/z):

487 (M⁺), 292 (M⁺ - C₁₀H₁₁O₄), 279 (M⁺ - C₁₄H₁₀NO), 208 (C₁₄H₁₀NO), 195 (C₁₀H₁₁O₄).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1630.

EXAMPLES 7 TO 56

The following compounds were synthesized from the appropriate starting materials prepared as described in the subsequent Preparations, following the general synthetic method given below.

General synthetic method:

0.793 g (2.88 mmole) of diphenylphosphoryl azide and then 0.449 g (1.60 mmole) of N-(3,4,5-trimethoxybenzoyl)piperazine were added to 7 ml of a methylene chloride solution containing 1.60 mmole of the respective 3,3-disubstituted-acrylic acid derivative (identified by the number of the Preparation shown in which it was prepared) and 0.67 ml (4.80 mmole) of triethylamine. The reaction mixture was then stirred for 3 hours at room temperature, after which it was diluted with 20 ml of methylene chloride. The resulting solution was washed with a saturated aqueous solution of sodium bicarbonate, with 10% w/v aqueous hydrochloric acid and with water, in that order, and the solution was then dried over anhydrous sodium sulphate. The solvent was distilled off, and the residue was subjected to moderate pressure liquid chromatography using two Lobar B columns connected in series. Elution with ethyl acetate removed the less polar impurities from the residue. Next, elution with mixtures of methylene chloride and methanol ranging from 100 : 1 to 100 : 2 by volume gave a desired N-(3,3-disubstituted-acryloyl)-N-(3,4,5-trimethoxybenzoyl)piperazine derivative, in a yield which varied from 50 to 99%. When the desired compound was obtained in the form of a non-crystalline solid, the compound was pulverized and dried; when it was obtained in a crystalline form, the compound was recrystallized from a suitable solvent (specified in the Example), to afford a sample for biological tests.

EXAMPLE 71-[(E)-3-(3,4-Dimethoxyphenyl)cinnamoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dimethoxyphenyl)cinnamic acid (prepared as described in Preparation 6) as a powder in a yield of 78%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.70 - 3.70 (8H, multiplet);

3.81 (3H, singlet);

3.84 (9H, singlet);

3.90 (3H, singlet);

6.25 (1H, singlet);

6.52 (2H, singlet);

6.76 - 6.88 (3H, multiplet);

7.27 - 7.42 (5H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1585, 1515, 1460, 1420, 1330, 1130.

Mass Spectrum (m/z):

546 (M⁺), 351, 279, 267, 195.

EXAMPLE 81-[(Z)-3-(3,4-Dimethoxyphenyl)cinnamoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dimethoxyphenyl)cinnamic acid (prepared as described in Preparation 7) as a powder in a yield of 88%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);
 3.85 (3H, singlet);
 3.86 (9H, singlet);
 3.92 (3H, singlet);
 5 6.22 (1H, singlet);
 6.55 (2H, singlet);
 6.80 (1H, doublet of doublets, $J = 8.30$ & 1.46 Hz);
 6.86 (1H, doublet, $J = 8.30$ Hz);
 6.86 - 6.88 (1H, multiplet);
 10 7.28 - 7.40 (5H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1585, 1515, 1460, 1420, 1335, 1130.
 Mass Spectrum (m/z):
 546 (M^+), 351, 279, 267, 195.

EXAMPLE 9

20 4-(3,4,5-Trimethoxybenzoyl)-1-[(E)-3-(3,4,5-trimethoxyphenyl)cinnamoyl]piperazine

Prepared from (E)-3-(3,4,5-trimethoxyphenyl)cinnamic acid (prepared as described in Preparation 10) as crystals, melting at $166 - 168^\circ \text{C}$ (after recrystallisation from a mixture of methylene chloride, diethyl ether and hexane), in a yield of 74%.

25 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.70 - 3.70 (8H, multiplet);

3.78 (3H, singlet);

3.846 (9H, singlet);

30 3.850 (3H, singlet);

3.87 (3H, singlet);

6.26 (1H, singlet);

6.47 (2H, singlet);

6.53 (2H, singlet);

35 7.28 - 7.42 (5H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1625, 1585, 1505, 1460, 1415, 1330, 1125.

Mass Spectrum (m/z):

576 (M^+), 381, 297, 279, 195.

EXAMPLE 10

45 4-(3,4,5-Trimethoxybenzoyl)-1-[(Z)-3-(3,4,5-trimethoxyphenyl)cinnamoyl]piperazine

Prepared from (Z)-3-(3,4,5-trimethoxyphenyl)cinnamic acid (prepared as described in Preparation 11) as crystals, melting at $149 - 151^\circ \text{C}$ (after recrystallisation from a mixture of methylene chloride, diethyl ether and hexane), in a yield of 79%.

50 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);

3.77 (6H, singlet);

3.85 (3H, singlet);

55 3.86 (6H, singlet);

3.89 (3H, singlet);

6.25 (1H, singlet);

6.53 (2H, singlet);

6.54 (2H, singlet);
 7.28 - 7.40 (5H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1585, 1505, 1460, 1415, 1335, 1125.

5

EXAMPLE 11

10

1-[(E)-3-(3-Methoxy-4-propoxyphenyl)cinnamoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3-methoxy-4-propoxyphenyl)cinnamic acid (prepared as described in Preparation 14) as a powder in a yield of 91%.

15 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.04 (3H, triplet, J = 7.32 Hz);
 1.88 (2H, multiplet);
 2.70 - 3.65 (8H, multiplet);
 3.79 (3H, singlet);
 20 3.84 (6H, singlet);
 3.85 (3H, singlet);
 3.99 (2H, triplet, J = 6.83 Hz);
 6.24 (1H, singlet);
 6.53 (2H, singlet);

25 6.75 - 6.85 (3H, multiplet);

7.27 - 7.43 (5H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1630, 1600, 1590, 1510, 1460, 1425, 1330, 1130.

Mass Spectrum (m/z):

30 574 (M^+), 531, 379, 295, 279, 195.

EXAMPLE 12

35

1-[(Z)-3-(3-Methoxy-4-propoxyphenyl)cinnamoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3-methoxy-4-propoxyphenyl)cinnamic acid (prepared as described in Preparation 15) as a powder in a yield of 91%.

40 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.06 (3H, triplet, J = 7.32 Hz);
 1.89 (2H, multiplet);
 2.80 - 3.70 (8H, multiplet);

45 3.78 (3H, singlet);

3.85 (3H, singlet);

3.86 (6H, singlet);

4.00 (3H, triplet, J = 6.84 Hz);

6.20 (1H, singlet);

50 6.55 (2H, singlet);

6.78 (1H, doublet of doublets, J = 8.30 & 1.46 Hz);

6.85 - 6.95 (2H, multiplet);

7.27 - 7.40 (5H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

55 1630, 1600, 1590, 1515, 1465, 1420, 1335, 1130.

Mass Spectrum (m/z):

574 (M^+), 531, 379, 295, 279, 195.

EXAMPLE 135 1-[(E)-3-(3,4-Dipropoxyphenyl)cinnamoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dipropoxyphenyl)cinnamic acid (prepared as described in Preparation 18) as a powder in a yield of 87%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 10 1.01 (3H, triplet, J = 7.33 Hz);
 1.05 (3H, triplet, J = 7.33 Hz);
 1.85 (4H, multiplet);
 2.70 - 3.70 (8H, multiplet);
 3.84 (9H, singlet);
 15 3.84 (6H, singlet);
 3.85 (3H, singlet);
 3.88 (2H, triplet, J = 6.83 Hz);
 3.97 (2H, triplet, J = 6.84 Hz);
 6.23 (1H, singlet);
 20 6.53 (2H, singlet);
 6.80 (3H, singlet);
 7.25 - 7.40 (5H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1600, 1590, 1510, 1460, 1425, 1330, 1130.

25 Mass Spectrum (m/z):

602 (M⁺), 559, 517, 407, 323, 195.

EXAMPLE 14

30

1-[(Z)-3-(3,4-Dipropoxyphenyl)cinnamoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

35 Prepared from (Z)-3-(3,4-dipropoxyphenyl)cinnamic acid (prepared as described in Preparation 19) as a powder in a yield of 88%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.01 (3H, triplet, J = 7.32 Hz);
 1.06 (3H, triplet, J = 7.32 Hz);
 40 1.70 - 1.95 (4H, multiplet);
 2.70 - 3.70 (8H, multiplet);
 3.85 (9H, singlet);
 3.85 - 3.92 (2H, multiplet);
 3.99 (2H, triplet, J = 6.84 Hz);
 45 6.19 (1H, multiplet);
 6.55 (2H, singlet);
 6.75 - 6.90 (3H, multiplet);
 7.28 - 7.40 (5H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

50 1630, 1600, 1590, 1510, 1460, 1420, 1330, 1130.

Mass Spectrum (m/z):

602 (M⁺), 559, 517, 407, 323, 195.

55

EXAMPLE 15

1-[(E)-3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (prepared as described in Preparation 22) as a powder in a yield of 89%.

5 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm: 3

2.80 - 3.70 (8H, multiplet);

3.82 (3H, singlet);

3.86 (9H, singlet);

3.90 (3H, singlet);

10 6.28 (1H, singlet);

6.56 (2H, singlet);

6.75 (1H, broad singlet);

6.81 (2H, broad singlet);

7.20 - 7.38 (4H, AB-like multiplet).

15 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1585, 1510, 1460, 1420, 1330, 1130.

Mass Spectrum (m/z):

580 (M⁺, ³⁵Cl), 385, 301, 279, 195.

20

EXAMPLE 1625 1-[(Z)-3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (prepared as described in Preparation 23) as a powder in a yield of 71%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

30 2.80 - 3.70 (8H, multiplet);

3.80 (3H, singlet);

3.86 (9H, singlet);

3.92 (3H, singlet);

6.20 (1H, singlet);

35 6.55 (2H, singlet);

6.78 (1H, doublet of doublets, J = 8.25 & 1.95 Hz);

6.86 (1H, doublet, J = 8.25 Hz);

6.81 - 6.87 (1H, multiplet);

7.20 - 7.36 (4H, AB-like multiplet).

40 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1635, 1595, 1515, 1465, 1425, 1335, 1135.

Mass Spectrum (m/z):

580 (M⁺, ³⁵Cl), 385, 301, 279, 195.

45

EXAMPLE 1750 1-[(Z)-3-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)-acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (prepared as described in Preparation 26) as a powder in a yield of 88%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

55 2.80 - 3.70 (8H, multiplet);

3.82 (3H, singlet);

3.86 (9H, singlet);

3.90 (3H, singlet);

6.29 (1H, singlet);
 6.57 (2H, singlet);
 6.77 (1H, broad singlet);
 6.82 (2H, multiplet);
 5 7.15 - 7.43 (4H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1600, 1590, 1515, 1460, 1420, 1330, 1130.
 Mass Spectrum (m/z):
 580 (M^+ , ^{35}Cl), 385, 301, 279, 195.

10

EXAMPLE 18

15

1-[(E)-3-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid (prepared as described in Preparation 27) as a powder in a yield of 90%.

20 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);
 3.81 (3H, singlet);
 3.86 (9H, singlet);
 3.92 (3H, singlet);
 25 6.22 (1H, singlet);
 6.55 (2H, singlet);
 6.78 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 6.85 (1H, multiplet);
 6.87 (1H, doublet, $J = 8.30$ Hz);
 30 7.13 - 7.38 (4H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1590, 1515, 1460, 1420, 1330, 1260, 1130.
 Mass Spectrum (m/z):
 580 (M^+ , ^{35}Cl), 385, 301, 279, 195.

35

EXAMPLE 19

40

1-[(E)-3-(4-Chlorophenyl)-3-(2,3-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(4-chlorophenyl)-3-(2,3-dimethoxyphenyl)acrylic acid (prepared as described in Preparation 30) as a powder in a yield of 85%.

45 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);
 3.57 (3H, singlet);
 3.86 (9H, singlet);
 3.87 (3H, singlet);
 50 6.17 (1H, singlet);
 6.55 (2H, singlet);
 6.75 (1H, doublet of doublets, $J = 7.81$ & 1.46 Hz);
 6.93 (1H, doublet of doublets, $J = 8.30$ & 1.46 Hz);
 7.04 (1H, triplet, $J = 8.30$ Hz);
 55 7.25 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.29 (2H, doublet of multiplets, $J = 8.79$ Hz).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1635, 1595, 1470, 1430, 1335, 1135.

Mass Spectrum (m/z):
580 (M⁺, ³⁵Cl), 549, 301, 195.

5

EXAMPLE 20

10 1-[(Z)-3-(4-Chlorophenyl)-3-(2,3-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(4-chlorophenyl)-3-(2,3-dimethoxyphenyl)acrylic acid (prepared as described in Preparation 31) as a powder in a yield of 94%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.90 - 3.70 (8H, multiplet);
15 3.855 (9H, singlet);
3.86 (6H, singlet);
6.38 (1H, singlet);
6.57 (2H, singlet);
6.86 (1H, doublet of doublets, J = 8.30 & 1.47 Hz);
20 6.96 (1H, doublet of doublets, J = 8.30 & 1.47 Hz);
7.07 (1H, triplet, J = 8.30 Hz);
7.20 (2H, doublet of multiplets, J = 8.79 Hz);
7.29 (2H, doublet of multiplets, J = 8.79 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

- 25 1630, 1585, 1460, 1420, 1330, 1125.

Mass Spectrum (m/z):
580 (M⁺, ³⁵Cl), 549, 301, 195.

30

EXAMPLE 21

35 1-[(Z)-3-(4-Chlorophenyl)-3-(4-isobutoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(4-chlorophenyl)-3-(4-isobutoxyphenyl)acrylic acid (prepared as described in Preparation 34) as crystals melting at 122 - 124 °C (after recrystallisation from a mixture of diethyl ether and hexane), in a yield of 75%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 40 1.03 (6H, doublet, J = 6.83 Hz);
2.09 (1H, multiplet);
2.80 - 3.65 (8H, multiplet);
3.73 (2H, doublet, J = 6.34 Hz);
3.86 (9H, singlet);
45 6.26 (1H, singlet);
6.56 (2H, singlet);
6.84 (2H, doublet of multiplets, J = 8.30 Hz);
7.17 (2H, doublet of multiplets, J = 8.30 Hz);
7.22 (2H, doublet of multiplets, J = 8.30 Hz);
50 7.34 (2H, doublet of multiplets, J = 8.30 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

1625, 1605, 1590, 1510, 1460, 1425, 1330, 1175, 1130.

Mass Spectrum (m/z):
592 (M⁺, ³⁵Cl), 535, 397, 313, 279, 257, 195.

55

EXAMPLE 22

1-[(E)-3-(4-Chlorophenyl)-3-(4-isobutoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(4-chlorophenyl)-3-(4-isobutoxyphenyl)acrylic acid (prepared as described in Preparation 35) as crystals melting at 128 - 129 °C (after recrystallisation from a mixture of diethyl ether and hexane), in a yield of 59%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.04 (6H, doublet, J = 6.84 Hz);
 - 2.10 (1H, multiplet);
 - 2.70 - 3.65 (8H, multiplet);
 - 3.75 (1H, doublet, J = 6.35 Hz);
 - 3.84 (6H, singlet);
 - 3.85 (3H, singlet);
 - 6.18 (1H, singlet);
 - 6.54 (2H, singlet);
 - 6.88 (2H, doublet of multiplets, J = 8.79 Hz);
 - 7.17 (2H, doublet of multiplets, J = 8.79 Hz);
 - 7.21 (2H, doublet of multiplets, J = 8.30 Hz);
 - 7.30 (2H, doublet of multiplets, J = 8.30 Hz).
- Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
- 1630, 1605, 1590, 1510, 1490, 1460, 1425, 1330, 1285, 1175, 1130.
- Mass Spectrum (m/z):
- 592 (M⁺, ³⁵Cl), 535, 397, 313, 279, 257, 195.

EXAMPLE 231-[(Z)-3-(4-Chlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(4-chlorophenyl)-3-(4-propoxyphenyl)acrylic acid (prepared as described in Preparation 38) as a powder in a yield of 76%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.04 (3H, triplet, J = 7.32 Hz);
 - 1.75 - 1.90 (2H, multiplet);
 - 2.80 - 3.65 (8H, multiplet);
 - 3.86 (9H, singlet);
 - 3.93 (2H, triplet, J = 6.84 Hz);
 - 6.28 (1H, singlet);
 - 6.56 (2H, singlet);
 - 6.85 (2H, doublet of multiplets, J = 8.79 Hz);
 - 7.17 (2H, doublet of multiplets, J = 8.79 Hz);
 - 7.22 (2H, doublet of multiplets, J = 8.79 Hz);
 - 7.34 (2H, doublet of multiplets, J = 8.79 Hz).
- Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
- 1630, 1605, 1590, 1510, 1460, 1425, 1330, 1130.
- Mass Spectrum (m/z):
- 578 (M⁺, ³⁵Cl), 535, 383, 299, 279, 195.

EXAMPLE 241-[(E)-3-(4-Chlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(4-chlorophenyl)-3-(4-propoxyphenyl)acrylic acid (prepared as described in Preparation 39) as a powder in a yield of 74%.

EP 0 395 446 A2

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.06 (3H, triplet, $J = 7.33$ Hz);
1.75 - 1.92 (2H, multiplet);
2.80 - 3.70 (8H, multiplet);
5 3.846 (6H, singlet);
3.850 (3H, singlet);
6.18 (1H, singlet);
6.54 (2H, singlet);
6.88 (2H, doublet of multiplets, $J = 8.78$ Hz);
10 7.17 (2H, doublet of multiplets, $J = 8.78$ Hz);
7.24 (2H, doublet of multiplets, $J = 8.30$ Hz);
7.30 (2H, doublet of multiplets, $J = 8.30$ Hz).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1630, 1605, 1590, 1510, 1460, 1420, 1330, 1130.
15 Mass Spectrum (m/z):
578 (M^+ , ^{35}Cl), 535, 383, 299, 279, 195.

EXAMPLE 25

20

1-[Bis(4-fluorophenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

- 25 Prepared from 3,3-bis(4-fluorophenyl)acrylic acid as a powder in a yield of 76%.
Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
2.70 - 3.70 (8H, multiplet);
3.85 (9H, singlet);
6.27 (1H, singlet);
30 6.56 (2H, singlet);
6.97 - 7.13 (4H, multiplet);
7.20 - 7.33 (4H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1630, 1600, 1585, 1505, 1460, 1420, 1330, 1125.
35 Mass Spectrum (m/z):
522 (M^+), 327, 279, 243, 195.

EXAMPLE 26

40

1-[(E)-3-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

- 45 Prepared from (E)-3-(4-fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid (prepared as described in Preparation 42) as crystals, melting at 195 - 197°C (after recrystallisation from a mixture of methylene chloride, diethyl ether and hexane), in a yield of 77%.
Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
2.80 - 3.70 (8H, multiplet);
50 3.79 (6H, singlet);
3.86 (9H, singlet);
3.87 (3H, singlet);
6.27 (1H, singlet);
6.45 (2H, singlet);
55 6.56 (2H, singlet);
7.05 - 7.13 (2H, multiplet);
7.25 - 7.33 (2H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1625, 1585, 1505, 1460, 1415, 1330, 1125.

Mass Spectrum (m/z):

594 (M⁺), 315, 279, 195.

5

EXAMPLE 27

10 1-[(Z)-3-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(4-fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid (prepared as described in Preparation 43) as crystals, melting at 130 - 132 °C (after recrystallisation from a mixture of methylene chloride and diethyl ether), in a yield of 78%.

15 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);

3.77 (6H, singlet);

3.85 (3H, singlet);

3.86 (6H, singlet);

20 3.89 (3H, singlet);

6.20 (1H, singlet);

6.51 (2H, singlet);

6.54 (2H, singlet);

7.00 - 7.09 (2H, multiplet);

25 7.26 - 7.35 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

1625, 1600, 1585, 1505, 1460, 1415, 1125.

Mass Spectrum (m/z):

594 (M⁺), 315, 279, 195.

30

EXAMPLE 28

35

1-[Bis(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from 3,3-bis(3,4-dimethoxyphenyl)acrylic acid as a powder in a yield of 74%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

40 2.80 - 3.70 (8H, multiplet);

3.81 (3H, singlet);

3.82 (3H, singlet);

3.86 (9H, singlet);

3.91 (3H, singlet);

45 3.92 (3H, singlet);

6.16 (1H, singlet);

6.56 (2H, singlet);

6.80 - 6.95 (6H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

50 1625, 1600, 1585, 1515, 1460, 1420, 1330, 1250, 1125.

Mass Spectrum (m/z):

606 (M⁺), 411, 327, 195.

55

EXAMPLE 29

1-[(E)-3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in Preparation 46) as a powder in a yield of 54%.

5 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);

3.81 (3H, singlet);

3.85 (12H, singlet);

3.90 (3H, singlet);

10 6.16 (1H, singlet);

6.55 (2H, singlet);

6.76 - 6.85 (3H, multiplet);

6.89 (2H, doublet of multiplets, J = 8.78 Hz);

7.22 (2H, doublet of multiplets, J = 8.78 Hz).

15 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1600, 1585, 1510, 1460, 1420, 1330, 1130.

Mass Spectrum (m/z):

576 (M⁺), 381, 297, 195.

20

EXAMPLE 30

25 1-[(Z)-3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in Preparation 47) as a powder in a yield of 73%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

30 2.90 - 3.70 (8H, multiplet);

3.80 (3H, singlet);

3.83 (3H, singlet);

3.86 (9H, singlet);

3.92 (3H, singlet);

35 6.15 (1H, singlet);

6.55 (2H, singlet);

6.78 - 6.91 (5H, multiplet);

7.12 - 7.26 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

40 1625, 1605, 1585, 1510, 1460, 1420, 1330, 1130.

Mass Spectrum (m/z):

576 (M⁺), 381, 297, 279, 195.

45

EXAMPLE 31

50 1-[(Z)-3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in Preparation 50) as a powder in a yield of 85%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

3.10 - 3.70 (8H, multiplet);

55 3.83 (3H, singlet);

3.857 (3H, singlet);

3.861 (6H, singlet);

6.32 (1H, singlet);

6.58 (2H, singlet);
 6.87 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.13 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 7.18 (2H, doublet of multiplets, $J = 8.79$ Hz);
 5 7.36 (1H, doublet, $J = 1.95$ Hz);
 7.45 (1H, doublet, $J = 8.30$ Hz).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1605, 1585, 1510, 1460, 1420, 1330, 1125.
 Mass Spectrum (m/z):
 10 584 (M^+ , ^{35}Cl), 389, 305, 279, 195.

EXAMPLE 32

15

1-[(E)-3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in
 20 Preparation 51) as a powder in a yield of 84%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm
 2.80 - 3.70 (8H, multiplet);
 3.85 (12H, singlet);
 6.21 (1H, singlet);
 25 6.54 (2H, singlet);
 6.90 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.10 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 7.18 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.38 (1H, doublet, $J = 1.95$ Hz);
 30 7.40 (1H, doublet, $J = 8.30$ Hz).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1605, 1585, 1510, 1460, 1420, 1330, 1130.
 Mass Spectrum (m/z):
 584 (M^+ , ^{35}Cl), 389, 305, 279, 195.

35

EXAMPLE 33

40

1-[(E)-3-(3,4-Dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acrylic acid (prepared as de-
 scribed in Preparation 54) as a powder in a yield of 74%.
 45 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 2.90 - 3.70 (8H, multiplet);
 3.82 (3H, singlet);
 3.848 (6H, singlet);
 3.853 (3H, singlet);
 50 3.91 (3H, singlet);
 6.37 (1H, singlet);
 6.56 (2H, singlet);
 6.77 (1H, broad singlet);
 6.79 - 6.88 (2H, multiplet);
 55 7.47 - 7.60 (3H, multiplet);
 7.60 - 7.71 (1H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1625, 1600, 1585, 1510, 1460, 1420, 1325, 1300, 1170, 1125.

Mass Spectrum (m/z):

614 (M⁺), 419, 335, 307, 279, 195.

5

EXAMPLE 34

10

1-[(Z)-3-(3,4-Dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acrylic acid (prepared as described in Preparation 55) as a powder in a yield of 50%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.80 - 3.70 (8H, multiplet);

15 3.81 (3H, singlet);

3.85 (3H, singlet);

3.86 (6H, singlet);

3.93 (3H, singlet);

6.26 (1H, singlet);

20 6.56 (2H, singlet);

6.78 (1H, doublet of doublets, J = 8.30 & 1.96 Hz);

6.86 (1H, multiplet);

6.87 (1H, doublet, J = 8.30 Hz); 7.43 - 7.53 (2H, multiplet);

7.53 - 7.67 (2H, multiplet).

25 Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

1625, 1600, 1585, 1515, 1460, 1420, 1325, 1255, 1165, 1125.

Mass Spectrum (m/z):

614 (M⁺), 419, 335, 307, 279, 195.

30

EXAMPLE 3535 1-[(E)-3-(3,4-Dimethoxyphenyl)-3-(4-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dimethoxyphenyl)-3-(4-methylphenyl)acrylic acid (prepared as described in Preparation 58) as a powder in a yield of 89%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

40 2.39 (3H, singlet);

2.80 - 3.70 (8H, multiplet);

3.81 (3H, singlet);

3.848 (6H, singlet);

3.851 (3H, singlet);

45 3.89 (3H, singlet);

6.20 (1H, singlet);

6.54 (2H, singlet);

6.79 (1H, broad singlet);

6.80 - 6.90 (2H, multiplet);

50 7.17 (4H, singlet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

1620, 1600, 1585, 1510, 1460, 1420, 1330, 1125.

Mass Spectrum (m/z):

560 (M⁺), 365, 281, 279, 195.

55

EXAMPLE 36

1-[(Z)-3-(3,4-Dimethoxyphenyl)-3-(4-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dimethoxyphenyl)-3-(4-methylphenyl)acrylic acid (prepared as described in Preparation 59) as a powder in a yield of 99%.

5 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.37 (3H, singlet);
 2.80 - 3.70 (8H, multiplet);
 3.80 (3H, singlet);
 3.85 (3H, singlet);
 10 3.86 (6H, singlet);
 3.91 (3H, singlet);
 6.19 (1H, singlet);
 6.55 (2H, singlet);
 6.80 (1H, doublet of doublets, J = 8.30 & 1.46 Hz);
 15 6.84 (1H, multiplet);
 6.85 (1H, doublet, J = 8.30 Hz);
 7.14 (2H, doublet, J = 8.30 Hz);
 7.19 (2H, doublet, J = 8.30 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

20 1625, 1585, 1510, 1460, 1420, 1330, 1255, 1125.

Mass Spectrum (m/z):

560 (M⁺), 365, 281, 279, 195.

25

EXAMPLE 371-[(Z)-3-(3,4-Dichlorophenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

30

Prepared from (Z)-3-(3,4-dichlorophenyl)-3-(3-methylphenyl)acrylic acid (prepared as described in Preparation 62) as a powder, in a yield of 91%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.34 (3H, singlet);
 35 2.90 - 3.70 (8H, multiplet);
 3.857 (3H, singlet);
 3.862 (6H, singlet);
 6.36 (1H, singlet);
 6.58 (2H, singlet);
 40 7.00 - 7.07 (2H, multiplet);
 7.13 (1H, doublet of doublets, J = 8.30 Hz);
 7.16 - 7.28 (2H, multiplet);
 7.36 (1H, doublet, J = 1.96 Hz);
 7.45 (1H, doublet, J = 8.30 Hz).

45 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1635, 1590, 1465, 1425, 1335, 1130.

Mass Spectrum (m/z):

568 (M⁺, ³⁵Cl), 373, 289, 279, 195.

50

EXAMPLE 3855 1-[(E)-3-(3,4-Dichlorophenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dichlorophenyl)-3-(3-methylphenyl)acrylic acid (prepared as described in Preparation 63) as a powder, in a yield of 92%.

EP 0 395 446 A2

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.35 (3H, singlet);
- 2.70 - 3.70 (8H, multiplet);
- 3.84 (6H, singlet);
- 5 3.85 (3H, singlet);
- 6.27 (1H, singlet);
- 6.53 (2H, singlet);
- 7.02 - 7.14 (3H, multiplet);
- 7.18 - 7.32 (2H, multiplet);
- 10 7.36 - 7.44 (3H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1630, 1610, 1590, 1465, 1425, 1335, 1130.

Mass Spectrum (m/z):

- 15 568 (M⁺, ³⁵Cl), 373, 289, 279, 195.

EXAMPLE 39

20 1-[(E)-3-(3,4-Dimethoxyphenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3,4-dimethoxyphenyl)-3-(3-methylphenyl)acrylic acid (prepared as described in Preparation 66) as a powder, in a yield of 83%.

25 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.34 (3H, singlet);
- 2.70 - 3.70 (8H, multiplet);
- 3.81 (3H, singlet);
- 3.846 (6H, singlet);
- 30 3.850 (3H, singlet);
- 3.90 (3H, singlet);
- 6.21 (1H, singlet);
- 6.54 (2H, singlet);
- 6.76 - 6.88 (3H, multiplet);
- 35 7.06 - 7.13 (2H, multiplet);
- 7.16 - 7.30 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1630, 1605, 1590, 1515, 1465, 1425, 1330, 1130.

Mass Spectrum (m/z):

- 40 560 (M⁺), 365, 281, 279, 195.

EXAMPLE 40

45 1-[(Z)-3-(3,4-Dimethoxyphenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dimethoxyphenyl)-3-(3-methylphenyl)acrylic acid (prepared as described in Preparation 67) as a powder, in a yield of 83%.

50 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.34 (3H, singlet);
- 2.80 - 3.70 (8H, multiplet);
- 3.80 (3H, singlet);
- 55 3.85 (3H, singlet);
- 3.86 (6H, singlet);
- 3.92 (3H, singlet);
- 6.20 (1H, singlet);

6.55 (2H, singlet);
 6.77 - 6.90 (3H, multiplet);
 7.06 - 7.28 (4H, multiplet);
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1600, 1590, 1515, 1465, 1425, 1330, 1260, 1130.
 Mass Spectrum (m/z):
 560 (M^+), 365, 281, 279, 195.

EXAMPLE 41

1-[3,3-Bis(3-chlorophenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from 3,3-bis(3-chlorophenyl)acrylic acid (prepared as described in Preparation 110) as a powder, in a yield of 86%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 2.80 - 3.70 (8H, multiplet);
 3.86 (9H, singlet);
 6.36 (1H, singlet);
 6.56 (2H, singlet);
 7.10 - 7.20 (2H, multiplet);
 7.27 - 7.43 (6H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1590, 1460, 1420, 1330, 1130.
 Mass Spectrum (m/z):
 554 (M^+ , ^{35}Cl), 359, 279, 275, 195.

EXAMPLE 42

1-[(Z)-3-(2-chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(2-Chlorophenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in Preparation 69) as a powder, in a yield of 91%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 2.80 - 3.80 (8H, multiplet);
 3.81 (3H, singlet);
 3.86 (9H, singlet);
 6.54 (1H, singlet);
 6.58 (2H, singlet);
 6.85 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.18 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.29 - 7.45 (4H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1605, 1585, 1510, 1460, 1420, 1330, 1130.
 Mass Spectrum (m/z):
 550 (M^+ , ^{35}Cl), 515, 279, 271, 195.

EXAMPLE 43

1-[(Z)-3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3-chlorophenyl)-3-(3-methoxyphenyl)acrylic acid (prepared as described in Preparation 72) as a powder, in a yield of 81%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.80 - 3.70 (8H, multiplet);
- 3.78 (3H, singlet);
- 3.85 (9H, singlet);
- 6.35 (1H, singlet);
- 6.56 (2H, singlet);
- 6.56 - 6.94 (3H, multiplet);
- 7.16 - 7.40 (5H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1600, 1585, 1460, 1420, 1330, 1125.

Mass Spectrum (m/z):

550 (M⁺, ³⁵Cl), 355, 279, 271, 195.

EXAMPLE 44

1-[(E)-3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3-chlorophenyl)-3-(3-methoxyphenyl)acrylic acid (prepared as described in Preparation 73) as a powder, in a yield of 82%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.80 - 3.70 (8H, multiplet);
- 3.77 (3H, singlet);
- 3.85 (9H, singlet);
- 6.29 (1H, singlet);
- 6.54 (2H, singlet);
- 6.80 - 6.87 (2H, multiplet);
- 6.90 - 6.97 (1H, multiplet);
- 7.12 - 7.19 (1H, multiplet);
- 7.22 - 7.37 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1630, 1600, 1585, 1460, 1420, 1330, 1125.

Mass Spectrum (m/z):

550 (M⁺, ³⁵Cl), 355, 279, 271, 195.

EXAMPLE 45

1-[(Z)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3-chlorophenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in Preparation 76) as a powder, in a yield of 81%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.80 - 3.70 (8H, multiplet);
- 3.83 (3H, singlet);
- 3.85 (9H, singlet);
- 6.28 (1H, singlet);
- 6.56 (2H, singlet);
- 6.86 (2H, doublet of multiplets, J = 8.79 Hz);
- 7.19 (2H, doublet of multiplets, J = 8.79 Hz);
- 7.26 - 7.40 (4H, multiplet);

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1625, 1605, 1585, 1510, 1460, 1420, 1330, 1125.

Mass Spectrum (m/z):

550 (M⁺, ³⁵Ct), 355, 279, 271, 195.

5

EXAMPLE 46

10 1-[(E)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylic acid (prepared as described in Preparation 77) as a powder, in a yield of 82%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

15 2.80 - 3.70 (8H, multiplet);

3.85 (12H, singlet);

6.21 (2H, singlet);

6.55 (2H, singlet);

6.90 (2H, doublet of multiplets, J = 8.79 Hz);

20 7.20 (2H, doublet of multiplets, J = 8.79 Hz);

7.12 - 7.36 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

1625, 1600, 1585, 1510, 1460, 1420, 1330, 1125.

Mass Spectrum (m/z):

25 550 (M⁺, ³⁵Ct), 355, 279, 271, 195.

EXAMPLE 47

30

1-[(Z)-3-(2-Naphthyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(2-naphthyl)-3-phenylacrylic acid (prepared as described in Preparation 113) as a powder, in a yield of 94%.

35 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.50 - 3.70 (8H, multiplet);

3.77 (3H, singlet);

3.82 (6H, singlet);

40 6.39 (3H, singlet);

7.28 - 7.40 (6H, multiplet);

7.46 - 7.57 (2H, multiplet);

7.78 - 7.90 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

45 1625, 1600, 1585, 1460, 1425, 1330, 1130.

Mass Spectrum (m/z):

536 (M⁺), 341, 279, 257, 195.

50

EXAMPLE 48

1-[(E)-3-(2-Naphthyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

55

Prepared from (E)-3-(2-naphthyl)-3-phenylacrylic acid (prepared as described in Preparation 114) as a powder, in a yield of 88%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.60 - 3.70 (8H, multiplet);
 3.85 (9H, singlet);
 6.44 (1H, singlet);
 6.54 (2H, singlet);
 5 7.30 - 7.54 (8H, multiplet);
 7.71 (1H, broad singlet);
 7.74 - 7.88 (3H, singlet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1625, 1605, 1595, 1460, 1420, 1330, 1125.
 10 Mass Spectrum (m/z):
 536 (M^+), 341, 279, 257, 195.

EXAMPLE 49

15

1-[(Z)-3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

- 20 Prepared from (Z)-3-(3,4-dichlorophenyl)-3-(4-propoxyphenyl)acrylic acid (prepared as described in Preparation 80), as a powder, in a yield of 84%
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 1.04 (3H, triplet, $J = 7.32$ Hz);
 1.73 - 1.90 (2H, multiplet);
 25 3.10 - 3.70 (8H, multiplet);
 3.86 (9H, multiplet);
 3.93 (2H, triplet, $J = 6.35$ Hz);
 6.31 (1H, singlet);
 6.58 (2H, singlet);
 30 6.86 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.13 (1H, doublet of doublets, $J = 8.30$ & 1.46 Hz);
 7.17 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.36 (1H, doublet, $J = 1.46$ Hz);
 7.45 (1H, doublet, $J = 8.30$ Hz).
 35 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1605, 1590, 1510, 1460, 1420, 1330, 1130.
 Mass Spectrum (m/z):
 612 (M^+ , ^{35}Cl), 569, 417, 333, 279, 195.

40

EXAMPLE 501-[(E)-3-(4-Ethoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

- Prepared from (E)-3-(4-ethoxy-3-methoxyphenyl)cinnamic acid (prepared as described in Preparation 84), as a powder, in a yield of 93%
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 50 1.47 (3H, triplet, $J = 6.84$ Hz);
 2.50 - 3.70 (8H, multiplet);
 3.80 (3H, singlet);
 3.84 (9H, singlet);
 4.11 (2H, quartet, $J = 6.84$ Hz);
 55 6.25 (1H, singlet);
 6.53 (2H, singlet);
 6.79 (1H, broad singlet);
 6.80 (2H, broad singlet);

7.27 - 7.34 (2H, multiplet);

7.34 - 7.41 (3H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1630, 1600, 1590, 1510, 1460, 1420, 1330, 1130. Mass Spectrum (m/z):

5 560 (M^+), 545, 365, 281, 195.

EXAMPLE 51

10

1-[(E)-3-(4-Butoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(4-butoxy-3-methoxyphenyl)cinnamic acid (prepared as described in Preparation
15 88), as a powder, in a yield of 79%

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

0.98 (3H, triplet, $J = 7.32$ Hz);

1.45 - 1.58 (2H, multiplet);

1.75 - 1.90 (2H, multiplet);

20 2.60 - 3.70 (8H, multiplet);

3.79 (3H, singlet);

3.84 (9H, singlet);

6.24 (1H, singlet);

6.53 (2H, singlet);

25 6.76 - 6.86 (3H, multiplet);

7.26 - 7.34 (2H, multiplet);

7.34 - 7.42 (3H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1625, 1600, 1590, 1510, 1460, 1420, 1330, 1130. Mass Spectrum (m/z):

30 588 (M^+), 545, 531, 393, 309, 279, 195.

EXAMPLE 52

35

1-[(Z)-3-(3,4-Dichlorophenyl)-3-(4-ethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (Z)-3-(3,4-dichlorophenyl)-3-(4-ethylphenyl)acrylic acid (prepared as described in Prep-
40 aration 91), as a powder, in a yield of 81%

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.25 (3H, triplet, $J = 7.32$ Hz);

2.67 (2H, quartet, $J = 7.32$ Hz);

3.00 - 3.70 (8H, multiplet);

45 3.86 (9H, multiplet);

6.36 (1H, singlet);

6.58 (2H, singlet);

7.13 (1H, doublet of doublets, $J = 8.30$ & 1.96 Hz);

7.12 - 7.22 (4H, multiplet);

50 7.36 (1H, doublet, $J = 1.96$ Hz); 7.45 (1H, doublet, $J = 8.30$ Hz). Infrared Absorption Spectrum (CHCl_3)

ν_{max} cm^{-1} :

1630, 1590, 1460, 1420, 1330, 1130.

Mass Spectrum (m/z):

582 (M^+ , ^{35}Cl), 387, 303, 279, 195.

55

EXAMPLE 53

1-[(E)-3-Phenyl-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

Prepared from (E)-3-(4-propoxyphenyl)cinnamic acid (prepared as described in Preparation 95), as a powder, in a yield of 78%

5 Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

- 1.03 (3H, triplet, J = 7 Hz);
- 1.50 - 2.15 (2H, multiplet);
- 2.80 - 3.70 (8H, multiplet);
- 3.83 (9H, singlet);
- 10 3.84 (2H, triplet, J = 7 Hz);
- 6.26 (1H, singlet);
- 6.56 (2H, singlet);
- 6.86 (2H, doublet of multiplets, J = 9 Hz);
- 7.24 (2H, doublet of multiplets, J = 9 Hz);
- 15 7.25 - 7.60 (5H, multiplet).

EXAMPLE 54

20

1-[(E)-3-(3,4-Methylenedioxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

25 Prepared from (E)-3-(3,4-methylenedioxyphenyl)cinnamic acid (prepared as described in Preparation 96), as a powder, in a yield of 94%

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

- 2.60 - 3.70 (8H, multiplet);
- 3.84 (9H, singlet);
- 30 5.98 (2H, singlet);
- 6.23 (1H, singlet);
- 6.55 (2H, singlet);
- 6.78 (3H, singlet);
- 7.20 - 7.60 (5H, multiplet).

35

EXAMPLE 55

40

1-[(E)-3-(3-Methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

45 Prepared from (E)-3-(3-methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acrylic acid (prepared as described in Preparation 100), as a powder, in a yield of 69%

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.04 (3H, triplet, J = 7.33 Hz);
- 1.80 - 1.95 (2H, multiplet);
- 2.34 (3H, singlet);
- 50 2.70 - 3.70 (8H, multiplet);
- 3.80 (3H, singlet);
- 3.85 (9H, singlet);
- 3.99 (2H, triplet, J = 6.84 Hz);
- 6.21 (1H, singlet);
- 55 6.54 (2H, singlet);
- 6.80 (3H, broad singlet);
- 7.05 - 7.13 (2H, multiplet);
- 7.16 - 7.30 (2H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1600, 1590, 1510, 1460, 1425, 1330, 1260, 1130.
 Mass Spectrum (m/z):
 588 (M^+), 545, 393, 309, 279, 195.

5

EXAMPLE 56

10

1-[3,3-Bis(3-Methylphenyl)acryloyl]-4-(3,4,5-trimethoxy-benzoyl)piperazine

Prepared from 3,3-bis(3-methylphenyl)acrylic acid (prepared as described in Preparation 103), as a powder, in a yield of 82%

15 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.34 (6H, singlet);
 2.60 - 3.70 (8H, multiplet);
 3.84 (9H, singlet);
 6.24 (1H, singlet);
 20 6.54 (2H, singlet);
 7.02 - 7.12 (4H, multiplet);
 7.13 - 7.29 (4H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1630, 1605, 1590, 1460, 1425, 1330, 1130.

25 Mass Spectrum (m/z):

514 (M^+ , ^{35}Cl), 319, 279, 235, 195.

EXAMPLE 57

30

1-[(E)-3,5-Diphenylpent-2-en-4-ynoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

35 Following a procedure similar to that described in Example 1, but using 0.900 g of (E)-3,5-diphenylpent-2-en-4-ynoic acid (prepared as described in Preparation 105), 1.574 g of the title compound was obtained as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

3.40 - 4.00 (8H, multiplet);
 40 3.83 (3H, singlet);
 3.85 (6H, singlet);
 6.59 (2H, singlet);
 6.74 (1H, singlet);
 7.3 - 7.8 (10H, multiplet).

45 Mass spectrum (m/z):

510 (M^+), 315, 279, 231, 195.

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1615, 1590, 1490, 1460, 1420, 1330, 1125.

50

Elemental analysis:	
Calculated for $\text{C}_{31}\text{H}_{30}\text{N}_2\text{O}_5$:	
Found:	C, 72.97%; H, 5.92%; N, 5.49%.
	C, 72.65%; H, 6.10%; N, 5.45%.

55

EXAMPLE 585 1-[(2E, 4Z)-3,5-Diphenylpent-2,4-dienoyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

0.025 g of 10% w/w palladium-on-barium sulphate and two drops of quinoline were added to 5ml of a methanol solution containing 0.250 g of 1-[(E)-3,5-diphenylpent-2-en-4-ynoyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine (prepared as described in Example 58). Hydrogen gas was introduced into the reaction mixture at room temperature and at atmospheric pressure. The reaction mixture was then shaken for 15 hours, after which the catalyst was filtered off and the solvent was removed by distillation under reduced pressure. The residue was subjected to moderate pressure liquid chromatography using a Lobar B column. 0.153 g of the title compound was obtained as a powder from those fractions eluted with mixtures of methylene chloride and ethyl acetate ranging from 3 : 2 to 1 : 3 by volume.

15 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.90 - 3.80 (8H, multiplet);

3.86 (3H, singlet);

3.87 (6H, singlet);

6.38 (1H, broad singlet);

20 6.58 (2H, singlet);

6.61 (1H, doublet of doublets, J = 12.20 & 1.95 Hz).

EXAMPLE 59

25

1-[3,3-Bis(4-methoxyphenyl)-2-methylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

30 Following a procedure similar to that described as the general synthetic method of Example 7, 0.673 g of the title compound was obtained as powder from 0.511 g of 3,3-bis(4-methoxyphenyl)-2-methylacrylic acid (prepared as described in Preparation 108).

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.00 (3H, singlet);

35 2.95 - 3.45 (8H, multiplet);

3.80 (3H, singlet);

3.82 (3H, singlet);

3.846 (6H, singlet);

3.851 (3H, singlet);

40 6.53 (2H, singlet);

6.75 - 7.20 (8H, multiplet).

Mass spectrum (m/z):

560 (M⁺); 545, 365, 281, 279, 195.

45

EXAMPLE 6050 1-(3,3-Diphenylacryloyl)-4-(3,4,5-trimethoxybenzenesulphonyl)piperazine

0.371 g of phosphorus pentachloride was added to 8 ml of a methylene chloride solution containing 0.400 g of 3-phenylcinnamic acid in an ice bath. The reaction solution was then stirred for 1 hour at 0° to 5° C, after which it was condensed by evaporation under reduced pressure. 10 ml of dry toluene were added to the residue, which was then evaporated to dryness under reduced pressure. The residue was dissolved in 5 ml of tetrahydrofuran, and this solution was added to a mixture of 0.564 g of N-(3,4,5-trimethoxybenzenesulphonyl)piperazine (prepared as described in Preparation 109), 0.300 g of sodium bicarbonate, 15 ml of tetrahydrofuran and 7.5 ml of water. The reaction solution was stirred for 30 minutes

at room temperature, and then poured into water, after which it was extracted twice with methylene chloride. The combined methylene chloride extracts were washed with 10% w/v aqueous hydrochloric acid, with a saturated aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order. They were then dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure. The residue was subjected to column chromatography using 20 g of silica gel. 0.750 g of the title compound was obtained as crystals, melting at 163°C - 165°C (after recrystallization from a mixture of ethyl acetate and hexane), from those fractions eluted with mixtures of methylene chloride and ethyl acetate ranging from 3 : 2 to 1 : 3 by volume.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.17 (2H, triplet, J = 4.76 Hz);
 2.81 (2H, triplet, J = 4.76 Hz);
 3.35 (2H, triplet, J = 4.76 Hz);
 3.64 (2H, triplet, J = 4.76 Hz);
 3.92 (6H, singlet);
 3.97 (3H, singlet);
 6.21 (1H, singlet);
 6.80 (2H, singlet);
 7.00 - 7.40 (10H, multiplet).

Mass spectrum (m/z):

- 522 (M⁺), 458, 315, 291, 231, 207.

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

1630, 1595, 1500, 1460, 1410, 1350, 1315, 1155, 1130.

25

Elemental analysis:	
Calculated for C ₂₈ H ₃₀ N ₂ O ₆ S:	
Found:	C, 64.35%; H, 5.79%; N, 5.36%; S, 6.14%.
	C, 64.60%; H, 5.94%; N, 5.35%; S, 6.27%.

30

EXAMPLE 61

35

1-(3-Phenylcinnamoyl)-4-[3,4,5-trimethoxy(thiobenzoyl)]piperazine

- 0.836 g of phosphorus pentachloride was added to 18 ml of a methylene chloride solution containing 0.900 g of 3-phenylcinnamic acid, in an ice bath. The mixture was then stirred for 1 hour at 0°C to 5°C. At the end of this time, the reaction mixture was evaporated to dryness under reduced pressure, and then 20 ml of dry toluene was added to the resulting residue; the mixture was then evaporated to dryness; this procedure was then repeated. The resulting residue was dissolved in 5 ml of tetrahydrofuran, and this solution was added to a mixture of 1.189 g of 1-(3,4,5-trimethoxythiobenzoyl)piperazine, 0.674 g of sodium bicarbonate, 25 ml of tetrahydrofuran and 12.5 ml of water, in an ice bath. The reaction mixture was then stirred for 30 minutes at room temperature, after which it was poured into water and extracted twice with methylene chloride. The methylene chloride extract was washed with 10% w/v aqueous hydrochloric acid, with a saturated aqueous solution of sodium bicarbonate and with water, in that order. It was then dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure. The residue was subjected to column chromatography through 40 g of silica gel. Those fractions eluted with a 3 : 1 by volume mixture of methylene chloride and ethyl acetate were collected, and the eluent removed, to give 1.860 g of the title compound as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 2.84 (1H, broad singlet);
 3.23 (1H, broad singlet);
 3.39 (1H, broad singlet);
 3.51 (2H, broad singlet);

EP 0 395 446 A2

3.69 (1H, broad singlet);
 3.76 (1H, broad singlet);
 3.82, 3.84 (together 9H, both singlets);
 4.17 (1H, broad singlet);
 5 6.27, 6.33 (1H, both singlets); 6.37, 6.44 (2H, both singlets); 7.20 - 7.50 (10H, multiplet).
 Mass spectrum (m/z):
 502 (M⁺), 469, 335, 295, 211, 207, 178, 167.
 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 1630, 1580, 1460, 1425, 1340, 1280, 1125.

10

EXAMPLE 62

15

1-[3,3-Bis(4-methoxyphenyl)acryloyl]-4-[3,4,5-trimethoxy(thiobenzoyl)]piperazine

Following a procedure similar to that described in Example 61, but using 0.400 g of 3,3-bis(4-methoxyphenyl)acrylic acid, 0.596 g of the title compound was obtained as a yellow powder.

20 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:
 2.96, 3.23, 3.45, 3.51, 4.20 (together 8H, 5 broad singlets);
 3.82 (6H, singlet);
 3.85 (9H, singlet);
 6.11, 6.16 (1H, both singlets);
 25 6.38, 6.45 (2H, both singlets);
 6.80 - 6.95 (4H, multiplet);
 7.10 - 7.30 (4H, multiplet).
 Mass spectrum (m/z):
 562 (M⁺), 529, 335, 295, 267, 227, 211.
 30 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 1625, 1605, 1585, 1510, 1460, 1425, 1340, 1280, 1170, 1125.

35

Elemental analysis:	
Calculated for C ₃₁ H ₃₄ N ₂ O ₆ S:	
Found:	C, 66.17%; H, 6.09%; N, 4.98%; S, 5.70%. C, 65.92%; H, 6.37%; N, 4.84%; S, 5.65%.

40

EXAMPLE 63

45

1-[3,3-Bis(4-fluorophenyl)]-4-[3,4,5-trimethoxy(thiobenzoyl)]piperazine

Following a procedure similar to that described in Example 61, but using 0.300 g of 3,3-bis(4-fluorophenyl)acrylic acid, 0.574 g of the title compound was obtained as a yellow powder.

50 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:
 3.04, 3.25, 3.52, 3.78, 4.21 (together 8H, 5 broad singlets);
 3.84 (9H, singlet);
 6.28 (1H, broad singlet);
 55 6.45 (2H, singlet);
 6.95 - 7.35 (8H, multiplet).
 Mass spectrum (m/z):
 538 (M⁺), 505, 335, 295, 243, 211.

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1630, 1600, 1580, 1505, 1460, 1425, 1340, 1125.

5

EXAMPLE 641-(3-Phenylcinnamoyl)-4-(3,4,5-trimethoxybenzyl)piperazine

10

Following a procedure similar to that described in Example 61, but using 0.500 g of 3-phenylcinnamic acid and 0.653 g of 1-(3,4,5-trimethoxybenzyl)piperazine, 0.897 g of the title compound was obtained as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

15 1.88 (2H, triplet, $J = 5.13$ Hz);2.25 (2H, triplet, $J = 5.13$ Hz);

3.28 (2H, multiplet);

3.28 (2H, singlet);

3.55 (2H, triplet) $J = 5.13$ Hz);

20 3.83 (3H, singlet);

3.84 (6H, singlet);

6.30 (1H, singlet);

6.46 (2H, singlet);

7.13 - 7.47 (10H, multiplet).

25 Mass spectrum (m/z):472 (M^+), 457, 291, 265, 207, 181.Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1630, 1595, 1460, 1440, 1345, 1125.

30

EXAMPLE 6535 1-[3,3-Diphenyl(thioacryloyl)]-4-[3,4,5-trimethoxy(thiobenzoyl)]piperazine

A solution of 1.000 g of 1-(3-phenylcinnamoyl)-4-[3,4,5-trimethoxy(thiobenzoyl)]piperazine (prepared as described in Example 61) in 10 ml of benzene and 0.805 g of Lawesson's Reagent {consisting mainly of

40 [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide] was heated under reflux for 2 hours. At the end of this time, the reaction mixture was cooled to room temperature, poured into water and extracted twice with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulphate, and concentrated by distillation under reduced pressure. The residue was purified by column chromatography through 30 g of silica gel eluted with a 3 : 1 by volume mixture of hexane and ethyl acetate, to give 1.010 g of the title compound as a yellow powder.

45 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.86 - 4.45 (8H, multiplet);

3.82 & 3.84 (together 9H, each singlet);

6.36 & 6.37 (together 2H, each singlet);

6.66 & 6.69 (together 1H, each singlet);

50 7.15 - 7.50 (10H, multiplet).

Mass spectrum (m/z):518 (M^+), 485; 351; 307.Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

55 1580, 1475, 1425, 1340, 1285, 1130.

EXAMPLE 66

1-[3,3-Bis(4-methoxyphenyl)thioacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

5

66(a) 1-[3,3-Bis(4-methoxyphenyl)acryloyl]piperazine

3.41 ml of diphenylphosphoryl azide and 1.09 ml of 1-formylpiperazine were added to a 60 ml of a
 10 methylene chloride solution of 3.00 g of 3,3-bis(4-methoxyphenyl)acrylic acid and 2.94 ml of triethylamine.
 The reaction mixture was then stirred for 2 hours at room temperature, after which it was poured into a
 saturated aqueous solution of sodium bicarbonate and extracted twice with methylene chloride. The
 combined extracts were washed with water, dried over anhydrous sodium sulphate and evaporated under
 reduced pressure. The residue was dissolved in 80 ml of methanol, and 40 ml of a 10% w/v aqueous
 15 solution of sodium hydroxide were added to the resulting solution. The reaction mixture was stirred for 18
 hours at room temperature and then poured into water; it was then extracted twice with methylene chloride.
 The combined extracts were washed with water, dried over anhydrous sodium sulphate and evaporated
 under reduced pressure. The residue was purified by column chromatography through 80 g of silica gel
 eluted with mixtures of methylene chloride and methanol ranging from 19 : 1 to 4 : 1 by volume to give 3.00
 20 g of 1-[3,3-bis(4-methoxyphenyl)acryloyl]piperazine as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

2.08 (1H, singlet);
 2.20 - 3.65 (8H, multiplet);
 3.80 (6H, singlet);
 25 6.13 (1H, singlet);
 6.70 - 7.40 (8H, multiplet).

66(b) 1-[3,3-Bis(4-methoxyphenyl)thioacryloyl]piperazine

30

1.155 g of the 1-[3,3-bis(4-methoxyphenyl)acryloyl]piperazine [prepared as described in step (a) above]
 were dissolved in 12 ml of benzene, and the resulting solution was heated under reflux for 2 hours with
 1.326 g of Lawesson's Reagent. At the end of this time, the reaction mixture was cooled to room
 temperature, after which it was poured into water and extracted twice with ethyl acetate. The combined
 35 extracts were washed with water, dried over anhydrous sodium sulphate, and concentrated by evaporation
 under reduced pressure. The residue was purified by column chromatography through 30 g of silica gel
 eluted with a 19 : 1 by volume mixture of methylene chloride and methanol, to give 1.177 g of 1-[3,3-bis(4-
 methoxyphenyl)thioacryloyl]piperazine as a powder.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

40 2.30 (2H, multiplet);
 2.80 (2H, multiplet);
 2.86 (1H, singlet);
 3.48 (2H, multiplet);
 3.80 (6H, singlet);
 45 4.16 (2H, multiplet);
 6.50 (1H, singlet);
 6.70 - 7.50 (8H, multiplet).

50

66(c) 1-[3,3-Bis(4-methoxyphenyl)thioacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine

1.049 g of 1-[3,3-bis(4-methoxyphenyl)thioacryloyl]piperazine [prepared as described in step (b) above]
 and 0.29 ml of triethylamine were dissolved in 30 ml of methylene chloride, and 0.157 g of 3,4,5-
 55 trimethoxybenzoyl chloride were added, whilst ice-cooling, to the resulting solution. The reaction mixture
 was then stirred for 1 hour at room temperature, after which it was poured into water and extracted twice
 with methylene chloride. The combined extracts were washed with 10% w/v aqueous hydrochloric acid, with
 a saturated aqueous solution of sodium bicarbonate and with water, in that order, after which they were

dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue was purified by column chromatography through 40 g of silica gel and by medium pressure liquid chromatography using a Lobar B column using mixtures of methylene chloride and ethyl acetate ranging from 9 : 1 to 4 : 1 by volume as eluent, to give 1.368 g of the title compound as a yellow powder.

5 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.75 - 3.30 (2H, multiplet);

3.40 - 3.70 (4H, multiplet);

3.83, 3.846 & 3.850 (together 15H, each singlet);

6.53 & 6.55 (together 3H, each singlet);

10 6.80 - 6.95 (4H, multiplet);

7.15 - 7.35 (4H, multiplet).

Mass spectrum (m/z):

562 (M^+); 529; 455; 367.

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

15 1630, 1605, 1585, 1510, 1460, 1420, 1330, 1280, 1170, 1125.

EXAMPLE 67

20

1-[3,3-Bis(4-methoxyphenyl)thioacryloyl]-4-[3,4,5-trimethoxy(thiobenzoyl)]piperazine

A procedure similar to that described in Example 65 was repeated, but using 0.790 g of 1-[3,3-Bis(4-methoxyphenyl)thioacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine (prepared as described in Example 66), to give 0.792 g of the title compound as a yellow powder.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.99, 3.46, 3.56, 3.72, 4.27 & 4.37 (together 8H, 6 broad singlets);

3.82, 3.83 & 3.85 (together 15H, each singlet);

30 6.39 & 6.46 (together 2H, each singlet);

6.51 & 6.55 (together 1H, each singlet);

6.80 - 6.95 (4H, multiplet);

7.10 - 7.37 (4H, multiplet).

Mass spectrum (m/z):

35 578 (M^+); 545; 513; 367.

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1605, 1580, 1510, 1460, 1425, 1335, 1280, 1170, 1125.

40

Elemental analysis:	
Calculated for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_5\text{S}_2$:	
Found:	C, 69.34%; H, 5.92%; N, 4.84%; S, 11.08%.
	C, 64.21%; H, 6.19%; N, 4.64%; S, 10.98%.

45

EXAMPLE 68

50

1-[3,3-Bis(3-chlorophenyl)acryloyl]-4-(3,4-dimethoxybenzoyl)piperazine

55 0.44 ml of diphenylphosphoryl azide and 0.545 g of 1-[3,3-bis(3-chlorophenyl)acryloyl]piperazine (prepared as described in Preparation 111) were added to 10 ml of a methylene chloride solution containing 0.25 g of 3,4-dimethoxybenzoic acid and 0.38 ml of triethylamine, and the reaction mixture was stirred for 16 hours at room temperature. At the end of this time, the mixture was washed with 10% w/v aqueous

hydrochloric acid, with a saturated aqueous solution of sodium bicarbonate and with water, in that order, after which it was dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, and the resulting residue was purified by medium pressure chromatography using two Lobar B columns eluted with mixtures of hexane and ethyl acetate ranging from 1 : 2 to 1 : 4 by

5 volume, to give 0.682 g of the title compound as a white powder.
Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.90 - 3.70 (8H, multiplet);
3.89 (3H, singlet);
3.90 (3H, singlet);
10 6.36 (1H, singlet);
6.85 (1H, doublet, J = 7.81 Hz);
6.92 (1H, doublet of doublets, J = 7.81 & 1.47 Hz);
6.95 (1H, doublet, J = 1.47 Hz);
7.10 - 7.20 (2H, multiplet);
15 7.24 - 7.42 (6H, multiplet).
Mass Spectrum (m/z):
524 (M⁺, ³⁵Cl), 359, 275, 249, 165.

20 EXAMPLE 69

25 1-[3,3-Bis(3-chlorophenyl)acryloyl]-4-(4-methoxybenzoyl)piperazine

0.25 g of p-methoxybenzoyl chloride were added to 10 ml of a methylene chloride solution containing 0.529 g of 1-[3,3-bis(3-chlorophenyl)acryloyl]piperazine (prepared as described in Preparation 111) and 0.41 ml of triethylamine, whilst ice-cooling, and the mixture was stirred at room temperature for 1 hour. The mixture was then worked up and purified as described in Example 68 to give 0.682 g of the title compound

30 as a powder. Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.90 - 3.70 (8H, multiplet);
3.83 (3H, singlet);
6.36 (1H, singlet);
6.90 (1H, doublet of multiplets, J = 8.79 Hz);
35 7.10 - 7.19 (2H, multiplet);
7.24 - 7.42 (8H, multiplet).
Mass Spectrum (m/z):
494 (M⁺, ³⁵Cl), 359, 275, 219, 135.

40

Elemental analysis:

Calculated for C₂₇H₂₄N₂O₃Cl₂:

45

Found:	C, 65.46%; H, 4.88%; N, 5.65%; Cl, 14.31%. C, 65.19%; H, 5.12%; N, 5.64%; Cl, 14.55%.
--------	--

50

PREPARATION 1

(E)- and (Z)-3-Phenyl-3-(2-thienyl)acrylic acids

55

100 ml of a tetrahydrofuran solution containing 26.30 g of triethyl phosphonoacetate were dropped over a period of 15 minutes at 8 - 10 °C into 400 ml of a tetrahydrofuran suspension containing 5.63 g of sodium hydride (as a 55% w/w suspension in mineral oil), in an ice bath. The reaction solution was then stirred for 1

hour at room temperature, after which 22.08 g of 2-benzoylthiophene were added. The reaction mixture was then heated under reflux for 21 hours, poured into 300 ml of water and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulphate and the solvent was distilled off under reduced pressure. 26.56 g of the resulting oily residue were dissolved in 450 ml of methanol, and 150 ml of a 10% w/v aqueous solution of sodium hydroxide were added thereto. The mixture was then stirred for 2 hours at room temperature. At the end of this time, the reaction solution was poured into 500 ml of water and washed with methylene chloride. Sufficient aqueous hydrochloric acid was added to the aqueous phase to adjust the pH to a value of 2, and then the mixture was extracted with methylene chloride. The extract was dried over anhydrous sodium sulphate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography. Elution with a 19 : 1 by volume mixture of methylene chloride and methanol gave at first 3.415 g of the less polar isomer A [thought to be the (Z)-isomer, Rf: 0.48 (silica gel, developing solvent: a 24 : 1 by volume mixture of methylene chloride and methanol)], and next 0.789 g of the other more polar isomer B [thought to be the (E)-isomer, Rf: 0.35 (silica gel, developing solvent: a 24 : 1 by volume mixture of methylene chloride and methanol)].

15 Isomer A:

Pale brown crystals, melting at 144 - 147 °C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 90 MHz) δ ppm:

6.34 (1H, singlet);

6.80 - 7.10 (2H, multiplet);

20 7.15 - 7.50 (6H, multiplet);

9.93 (1H, broad singlet).

Mass spectrum (m/z):

230 (M⁺).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

25 1685, 1610, 1595.

Elemental analysis:	
Calculated for C ₁₃ H ₁₀ O ₂ S:	
Found:	C, 67.80%; H, 4.38%; S, 13.92%.
	C, 67.71%; H, 4.12%; N, 13.88%.

35 Isomer B:

Pale brown crystals, melting at 152 - 155 °C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 90 MHz) δ ppm:

6.18 (1H, singlet);

6.95 - 7.15 (1H, multiplet);

40 7.15 - 7.55 (7H, multiplet);

10.66 (1H, broad singlet).

Mass spectrum (m/z):

230 (M⁺).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

45 1690, 1595.

PREPARATION 2

50

Ethyl (E)- and (Z)-3-phenyl-3-(4-pyridyl)acrylates

100 ml of a tetrahydrofuran solution containing 26.92 g of triethyl phosphonoacetate were dropped over a period of 20 minutes into 400 ml of a tetrahydrofuran suspension containing 5.76 g of sodium hydride (as a 55% w/w suspension in mineral oil), at 8 - 10 °C in an ice bath. The reaction solution was then stirred for 1 hour at room temperature, after which 22.00 g of 4-benzoylpyridine were added. After the mixture had been stirred for a further 3 hours, the reaction solution was poured into 300 ml of water and extracted with

ethyl acetate. The extract was dried over anhydrous sodium sulphate and then the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography. Elution with mixtures of hexane and methylene chloride ranging from 3 : 1 to 1 : 1 by volume gave at first 10.047 g of the less polar isomer C [thought to be the (Z)-isomer, Rf: 0.63 (silica gel, developing solvent: a 49 : 1 by volume mixture of methylene chloride and methanol)], and next elution with mixtures of hexane and methylene chloride ranging from 1 : 1 to 0 : 1 by volume gave 16.603 g of the other more polar isomer D [thought to be the (E)-isomer, Rf: 0.55 (silica gel, developing solvent: a 49 : 1 by volume mixture of methylene chloride and methanol)].

Isomer C:

10 Colourless oil.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 90 MHz) δ ppm:

1.11 (3H, triplet, $J = 7.5$ Hz);

4.07 (2H, quartet, $J = 7.5$ Hz);

6.48 (1H, singlet);

15 7.05 - 7.55 (7H, multiplet);

8.40 - 8.90 (2H, multiplet).

Mass spectrum (m/z):

253 (M^+), 208 ($M^+ - \text{C}_2\text{H}_5\text{O}$).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

20 1720.

Elemental analysis:	
Calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_2$:	
Found:	C, 75.87%; H, 5.97%; N, 5.53%. C, 75.91%; H, 6.26%; N, 5.48%.

30 Isomer D:

Colourless crystals, melting at 101 - 102 °C.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 90 MHz) δ ppm:

1.12 (3H, triplet, $J = 7.5$ Hz);

4.05 (2H, quartet, $J = 7.5$ Hz);

35 6.46 (1H, singlet);

7.05 - 7.50 (7H, multiplet);

8.50 - 8.85 (2H, multiplet).

Mass spectrum (m/z):

253 (M^+), 208 ($M^+ - \text{C}_2\text{H}_5\text{O}$).

40 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1715.

Elemental analysis:	
Calculated for $\text{C}_{16}\text{H}_{15}\text{NO}_2$:	
Found:	C, 75.87%; H, 5.97%; N, 5.53%. C, 75.86%; H, 5.86%; N, 5.59%.

PREPARATION 3

(E)-3-Phenyl-3-(4-pyridyl)acrylic acid

20 ml of a 10% w/v aqueous solution of sodium hydroxide were added to 35 ml of a methanol solution containing 3.41 g of ethyl (E)-3-phenyl-3-(4-pyridyl)acrylate (prepared as described in Preparation 2), and the mixture was stirred for 1 hour at room temperature. At the end of this time, the reaction solution was poured into 50 ml of water and washed with methylene chloride. Sufficient hydrochloric acid was added to the aqueous phase to adjust the pH to a value of 2.8. The resulting precipitate was collected, giving 2.131 g of the title compound, as a white powder, melting at 239 - 241 °C.

Nuclear Magnetic Resonance Spectrum (hexadeuterated dimethyl sulfoxide, 90 MHz) δ ppm:

6.51 (1H, singlet);

7.15 - 7.55 (7H, multiplet);

8.45 - 8.80 (2H, multiplet).

Mass spectrum (m/z):

225 (M^+); 180 ($M^+ - COOH$).

Infrared Absorption Spectrum (Nujol - trade mark) ν_{max} cm^{-1} :

1697; 1625; 1602.

PREPARATIONS 4 to 103

General Synthesis of 3,3-Diphenylacrylic Acid Derivatives According to Heck's Reaction

This follows essentially the same method as that reported by Heck et al. [J. Org. Chem. 43, 2952 (1978)], in which a coupling reaction of an (E)-acrylic acid ester having a substituted group, R^1 , at its 3-position with an iodine compound having a substituted group, R^2 , was conducted. A mixture of 20 mmole of an (E)-acrylic acid ethyl ester having R^1 at its 3-position, 30 mmole of an aryl iodide represented by the general formula R^2-I , 4.17 ml of triethylamine, 0.270 g of palladium acetate and 8 ml of acetonitrile was put into a sealed tube, and heated for 18 hours in an oil bath at 100 °C. The mixture was stood to allow it to cool, after which it was diluted with 30 ml of ethyl acetate, and then washed with 10% w/v aqueous hydrochloric acid, with a saturated aqueous solution of sodium bicarbonate and with a saturated aqueous solution of sodium chloride, in that order. The organic phase was dried and condensed by evaporation under reduced pressure. The residue was subjected to flash column chromatography using silica gel (about 400 Tyler mesh, 400 g), and medium pressure liquid chromatography using a Lobar C column (Type Si-60). Elution with mixtures of methylene chloride, diethyl ether and hexane ranging from 1 : 1 : 5 to 1 : 1 : 4 by volume gave separately the (E)-isomer and the (Z)-isomer of a 3,3-disubstituted ethyl acrylate. Where two isomers were produced, each is mentioned in a separate Preparation, but the isomer eluted earlier in the chromatographic procedure mentioned above appears in the first of the pair of Preparations. Toluene was employed as the eluent for separation of the isomers of the compounds of Preparations 32/33, and 36/37. The isolated (E)- or (Z)-3,3-diphenylacrylic acid ethyl ester (4 mmole) was dissolved in a mixture of 12 ml of dioxane and 12 ml of methanol, and 5 ml of a 10% w/v aqueous solution of sodium hydroxide were added for hydrolysis. The reaction mixture was stirred for 18 hours at room temperature, and then the solvent was distilled off. The residue was diluted with 20 ml of water and washed with ethyl acetate. Sufficient 10% w/v aqueous hydrochloric acid was added to the aqueous phase to adjust the pH to a value of 2, and then the mixture was extracted twice with methylene chloride. The combined methylene chloride extracts were washed with water and then dried over anhydrous sodium sulphate. The desired 3,3-disubstituted acrylic acid was obtained as a solid. The results are summarized below.

The ester compounds of Preparations 96 and 97 could not, however, be separated by the method described above. Accordingly, they were separated by the following procedure:

The mixture of the compounds of Preparations 96 and 97 was hydrolyzed as described above. The mixture of the acid compounds thus obtained was then washed with methylene chloride, and the insoluble material was recrystallized from a mixture of diethyl ether and tetrahydrofuran, to give the compound of Preparation 96 (believed to be the E-isomer). The methylene chloride washings were condensed by distillation under reduced pressure, and the residue was recrystallized from a mixture of methylene chloride and hexane, to give the compound of Preparation 97 (believed to be the Z-isomer).

PREPARATION 4

Ethyl (E)-3-(3,4-dimethoxyphenyl)cinnamate

Prepared as an oil in a yield of 14%

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 5 1.10 (3H, triplet, $J = 7.32$ Hz);
 3.82 (3H, singlet);
 3.88 (3H, singlet);
 4.04 (2H, quartet, $J = 7.32$ Hz);
 6.32 (1H, singlet);
 10 6.74 - 6.84 (2H, multiplet);
 6.89 (1H, broad singlet);
 7.16 - 7.25 (2H, multiplet);
 7.34 - 7.42 (2H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

- 15 1705, 1595, 1580, 1510, 1465, 1160, 1135.

Mass Spectrum (m/z):

312 (M^+), 297, 283, 267, 240.

PREPARATION 5Ethyl (Z)-3-(3,4-dimethoxyphenyl)cinnamate

- 25 Prepared as crystals, melting at $93 - 95^\circ\text{C}$ (after recrystallisation from a mixture of diethyl ether and hexane), in a yield of 21%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.16 (3H, triplet, $J = 7.32$ Hz);
 30 3.81 (3H, singlet);
 3.92 (3H, singlet);
 4.09 (2H, quartet, $J = 7.32$ Hz);
 6.29 (1H, singlet);
 6.72 (1H, doublet, $J = 1.95$ Hz);
 35 6.82 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 6.88 (1H, doublet, $J = 8.30$ Hz);
 7.30 - 7.14 (5H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

- 1710, 1605, 1585, 1515, 1465, 1445, 1160, 1135. Mass Spectrum (m/z):
 40 312 (M^+), 297, 283, 267, 240.

PREPARATION 6(E)-3-(3,4-Dimethoxyphenyl)cinnamic acid

- 45 Prepared as crystals, melting at $178 - 181^\circ\text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 98%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 3.81 (3H, singlet);
 3.88 (3H, singlet);
 6.28 (1H, singlet);
 55 6.75 - 6.83 (2H, multiplet);
 6.86 (1H, broad singlet);
 7.17 - 7.25 (2H, multiplet); 7.33 - 7.43 (3H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

EP 0 395 446 A2

2400 - 3600 (broad), 1690, 1595, 1515, 1260, 1135.

Mass Spectrum (m/z):

284 (M^+), 269, 267, 239.

5

PREPARATION 7

10 (Z)-3-(3,4-Dimethoxyphenyl)cinnamic acid

Prepared as crystals, melting at 162 - 164 °C (after recrystallisation from a mixture of diethyl ether and hexane), in a yield of 99%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

15 3.80 (3H, singlet);

3.92 (3H, singlet);

6.26 (1H, singlet);

6.75 (1H, doublet, $J = 1.95$ Hz);

6.80 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);

20 6.87 (1H, doublet, $J = 8.30$ Hz);

7.27 - 7.43 (5H, multiplet).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1690, 1605, 1515, 1255, 1135.

Mass Spectrum (m/z):

25 284 (M^+), 269, 267, 239.

PREPARATION 8

30

Ethyl (E)-3-(3,4,5-trimethoxyphenyl)cinnamate

Prepared as crystals, melting at 119 - 121 °C (after recrystallisation from a mixture of diethyl ether, methylene chloride and hexane), in a yield of 19%.

35 Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.11 (3H, triplet, $J = 7.32$ Hz);

3.77 (6H, singlet);

3.87 (3H, singlet);

40 4.05 (2H, quartet, $J = 7.32$ Hz);

6.32 (1H, singlet);

6.51 (2H, singlet);

7.18 - 7.24 (2H, multiplet);

7.35 - 7.41 (3H, multiplet).

45 Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

1710, 1615, 1580, 1500, 1460, 1415, 1160, 1125.

Mass Spectrum (m/z):

342 (M^+), 327, 313, 299, 297.

50

PREPARATION 9

55 Ethyl (Z)-3-(3,4,5-trimethoxyphenyl)cinnamate

Prepared as crystals, melting at 96 - 98 °C (after recrystallisation from a mixture of methylene chloride and diethyl ether), in a yield of 35%.

EP 0 395 446 A2

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1. 14 (3H, triplet, $J = 7.33$ Hz);
3.80 (6H, singlet);
3.90 (3H, singlet);
5 4.08 (2H, quartet, $J = 7.33$ Hz);
6.32 (1H, singlet);
6.43 (2H, singlet);
7.31 - 7.40 (5H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
10 1710, 1610, 1585, 1500, 1460, 1410, 1300, 1170, 1125.
Mass Spectrum (m/z):
342 (M^+), 327, 313, 299, 297.

15

PREPARATION 10

(E)-3-(3,4,5-Trimethoxyphenyl)cinnamic acid

20

Prepared as crystals, melting at $202 - 206^\circ \text{C}$ (after recrystallisation from a mixture of diethyl ether and methylene chloride), in a yield of 100%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 3.76 (6H, singlet);
25 3.87 (3H, singlet);
6.30 (1H, singlet);
6.49 (2H, singlet);
7.19 - 7.25 (2H, multiplet);
7.35 - 7.41 (3H, multiplet).
30 Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1} :
2400 - 3400 (broad), 1688, 1610, 1578, 1502, 1241, 1200, 1129.
Mass Spectrum (m/z):
314 (M^+), 299.

35

PREPARATION 11

40 (Z)-3-(3,4,5-Trimethoxyphenyl)cinnamic acid

Prepared as crystals, melting at $203 - 205^\circ \text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 100%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 45 3.78 (6H, singlet);
3.91 (3H, singlet);
6.30 (1H, singlet);
6.44 (2H, singlet);
7.28 - 7.43 (5H, multiplet).
50 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
2400 - 3600 (broad), 1690, 1610, 1580, 1500, 1460, 1410, 1365, 1125.
Mass Spectrum (m/z):
314 (M^+), 299.

55

PREPARATION 12

Ethyl (E)-3-(3-methoxy-4-propoxyphenyl)cinnamate

Prepared as crystals, melting at 66 - 68 °C (after recrystallisation from hexane), in a yield of 24%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 5 1.03 (3H, triplet, J = 7.32 Hz);
 1.10 (3H, triplet, J = 7.33 Hz);
 1.80 - 1.95 (2H, multiplet);
 3.81 (3H, singlet);
 3.98 (2H, triplet, J = 6.84 Hz);
 10 4.03 (2H, quartet, J = 7.33 Hz);
 6.31 (1H, singlet);
 6.77 (1H, singlet);
 6.78 (1H, singlet);
 6.89 (1H, singlet);
 15 7.16 - 7.25 (2H, multiplet);
 7.35 - 7.45 (3H, multiplet).
 Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:
 1710, 1600, 1520, 1470, 1375, 1260, 1160, 1140.
 Mass Spectrum (m/z):
 20 340 (M⁺), 298, 269, 253, 226.

PREPARATION 13

25

Ethyl (Z)-3-(3-methoxy-4-propoxyphenyl)cinnamate

Prepared as an oil in a yield of 37%.

- 30 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:
 1.05 (3H, triplet, J = 7.32 Hz);
 1.15 (3H, triplet, J = 7.32 Hz);
 1.80 - 2.00 (2H, multiplet);
 3.79 (3H, singlet);
 35 4.01 (2H, triplet, J = 6.83 Hz);
 4.08 (2H, quartet, J = 7.32 Hz);
 6.27 (1H, singlet);
 6.72 (1H, doublet, J = 1.95 Hz);
 6.78 (1H, doublet of doublets, J = 8.30 & 1.95 Hz);
 40 6.87 (1H, doublet, J = 8.30 Hz);
 7.30 - 7.42 (5H, multiplet).
 Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:
 1710, 1610, 1515, 1470, 1375, 1260, 1170, 1140.
 Mass Spectrum (m/z):
 45 340 (M⁺), 298, 269, 253, 226.

PREPARATION 14

50

(E)-3-(3-Methoxy-4-propoxyphenyl)cinnamic acid

Prepared as crystals, melting at 147 - 150 °C (after recrystallisation from a mixture of methylene

55 chloride and hexane), in a yield of 94%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.03 (3H, triplet, J = 7.33 Hz);
 1.75 - 2.00 (2H, multiplet);

- 3.79 (3H, singlet);
 3.98 (2H, triplet, $J = 6.84$ Hz);
 6.28 (1H, singlet);
 6.73 - 6.80 (2H, multiplet);
 5 6.85 (1H, broad singlet);
 7.15 - 7.25 (2H, multiplet).
 7.33 - 7.40 (3H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 2400 - 3600 (broad), 1690, 1610, 1595, 1580, 1510, 1465, 1260, 1180, 1135.
 10 Mass Spectrum (m/z):
 312 (M^+), 270, 253, 225.

PREPARATION 15

15

(Z)-3-(3-Methoxy-4-propoxyphenyl)cinnamic acid

- 20 Prepared as crystals, melting at $139 - 142^\circ\text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 93%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 1.06 (3H, triplet, $J = 7.33$ Hz);
 1.80 - 2.00 (2H, multiplet);
 25 3.79 (3H, singlet);
 4.01 (2H, triplet, $J = 6.84$ Hz);
 6.24 (1H, singlet);
 6.29 - 6.79 (2H, multiplet);
 6.85 (1H, doublet of doublets, $J = 8.33$ & 1.47 Hz);
 30 7.25 - 7.45 (5H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 2400 - 3600 (broad), 1690, 1600, 1575, 1510, 1465, 1445, 1410, 1250, 1130.
 Mass Spectrum (m/z):
 312 (M^+), 270, 253, 225.

35

PREPARATION 16

40

Ethyl (E)-3-(3,4-dipropoxyphenyl)cinnamate

- Prepared as an oil in a yield of 16%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 45 1.01 (3H, triplet, $J = 7.33$ Hz);
 1.03 (3H, triplet, $J = 7.33$ Hz);
 1.10 (3H, triplet, $J = 7.33$ Hz);
 1.70 - 1.95 (4H, multiplet);
 3.90 (2H, triplet, $J = 6.83$ Hz);
 50 3.96 (2H, triplet, $J = 6.83$ Hz);
 4.03 (2H, quartet, $J = 7.33$ Hz);
 6.30 (1H, singlet);
 6.72 - 6.80 (2H, multiplet);
 6.90 (1H, broad singlet);
 55 7.15 - 7.25 (2H, multiplet).
 7.30 - 7.45 (3H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1705, 1595, 1510, 1470, 1370, 1260, 1160, 1130.

Mass Spectrum (m/z):
368 (M^+), 326, 323, 284.

5

PREPARATION 17Ethyl (Z)-3-(3,4-dipropoxyphenyl)cinnamate

10

Prepared as an oil in a yield of 25%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

- 1.00 (3H, triplet, $J = 7.32$ Hz);
- 1.06 (3H, triplet, $J = 7.32$ Hz);
- 15 1.15 (3H, triplet, $J = 7.32$ Hz);
- 1.70 - 1.95 (4H, multiplet);
- 3.89 (2H, triplet, $J = 6.84$ Hz);
- 4.00 (2H, triplet, $J = 6.84$ Hz);
- 4.08 (2H, quartet, $J = 7.32$ Hz);
- 20 6.26 (1H, singlet);
- 6.73 (1H, doublet, $J = 1.95$ Hz);
- 6.77 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
- 6.86 (1H, doublet, $J = 8.30$ Hz);
- 7.25 - 7.40 (5H, multiplet).

- 25 Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :
1710, 1605, 1510, 1470, 1445, 1370, 1260, 1160, 1130.

Mass Spectrum (m/z):
368 (M^+), 326, 323, 284.

30

PREPARATION 18(E)-3-(3,4-Dipropoxyphenyl)cinnamic acid

35

Prepared as crystals, melting at $102 - 103^\circ C$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 92%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

- 40 1.00 (3H, triplet, $J = 7.32$ Hz);
 - 1.03 (3H, triplet, $J = 7.32$ Hz);
 - 1.70 - 1.95 (4H, multiplet);
 - 3.89 (2H, triplet, $J = 6.83$ Hz);
 - 3.96 (2H, triplet, $J = 6.84$ Hz);
 - 45 4.06 (2H, quartet, $J = 7.32$ Hz);
 - 6.26 (1H, singlet);
 - 6.74 (1H, doublet of doublets, $J = 8.30$ & 1.96 Hz);
 - 6.78 (1H, doublet, $J = 8.30$ Hz);
 - 6.86 (1H, doublet, $J = 1.96$ Hz);
 - 50 7.15 - 7.25 (2H, multiplet);
 - 7.30 - 7.40 (3H, multiplet).
- Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :
2400 - 3600 (broad), 1690, 1610, 1595, 1580, 1510, 1425, 1260, 1135.
- Mass Spectrum (m/z):
55 340 (M^+), 298, 256, 239.

PREPARATION 19

(Z)-3-(3,4-Dipropoxyphenyl)cinnamic acid

5

Prepared as crystals, melting at 120 - 123 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 94%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.00 (3H, triplet, J = 7.33 Hz);
 10 1.06 (3H, triplet, J = 7.32 Hz);
 1.70 - 1.95 (4H, multiplet);
 3.89 (2H, triplet, J = 6.84 Hz);
 4.00 (2H, triplet, J = 6.84 Hz);
 6.23 (1H, singlet);
 15 6.73 - 6.80 (2H, multiplet);
 6.83 - 6.87 (1H, multiplet);
 7.25 - 7.45 (5H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

- 2400 - 3600 (broad), 1695, 1610, 1515, 1260, 1135. Mass Spectrum (m/z):
 20 340 (M⁺), 298, 256, 239.

PREPARATION 20

25

Ethyl (E)-3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylate

- Prepared as crystals, melting at 83 - 84 °C (after recrystallisation from a mixture of diethyl ether and
 30 hexane), in a yield of 14%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.15 (3H, triplet, J = 7.32 Hz);
 3.84 (3H, singlet);
 3.89 (3H, singlet);
 35 4.06 (2H, quartet, J = 7.32 Hz);
 6.31 (1H, singlet);
 6.76 (1H, doublet of doublets, J = 8.79 & 1.95 Hz);
 6.80 (1H, doublet, J = 8.79 Hz);
 6.86 (1H, doublet, J = 1.95 Hz);
 40 7.15 (2H, doublet of multiplets, J = 8.79 Hz);
 7.36 (2H, doublet of multiplets, J = 8.79 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

- 1705, 1615, 1595, 1580, 1510, 1460, 1370, 1290, 1160, 1135.
 Mass Spectrum (m/z):
 45 346 (M⁺, ³⁵Cl), 317, 301, 274.

PREPARATION 21

50

Ethyl (Z)-3-(4-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylate

- Prepared as crystals, melting at 67 - 69 °C (after recrystallisation from a mixture of diethyl ether and
 55 hexane), in a yield of 22%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.16 (3H, triplet, J = 7.32 Hz);
 3.81 (3H, singlet);

- 3.91 (3H, singlet);
 6.26 (1H, singlet);
 6.70 (1H, doublet, $J = 1.95$ Hz);
 6.79 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 5 6.88 (1H, doublet, $J = 8.30$ Hz);
 7.12 - 7.40 (4H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1710, 1600, 1590, 1515, 1490, 1460, 1255, 1170, 1135.
 Mass Spectrum (m/z):
 10 346 (M^+ , ^{35}Cl), 317, 301, 274.

PREPARATION 22

15

(E)-3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid

- Prepared as crystals, melting at $164 - 165^\circ \text{C}$ (after recrystallisation from a mixture of methylene
 20 chloride and hexane), in a yield of 85%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 3.83 (3H, singlet);
 3.89 (3H, singlet);
 6.29 (1H, singlet);
 25 6.76 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 6.80 (1H, doublet, $J = 8.30$ Hz);
 6.84 (1H, doublet, $J = 1.95$ Hz);
 7.15 (2H, doublet of multiplets, $J = 8.30$ Hz);
 7.35 (2H, doublet of multiplets, $J = 8.30$ Hz).
 30 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 2400 - 3600 (broad), 1690, 1610, 1595, 1515, 1465, 1260, 1175, 1135.
 Mass Spectrum (m/z):
 318 (M^+), 303, 243.

35

PREPARATION 23(Z)-3-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid

- Prepared as crystals, melting at $188 - 190^\circ \text{C}$ (after recrystallisation from a mixture of methylene
 chloride and hexane), in a yield of 91%.
 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 45 3.80 (3H, singlet);
 3.92 (3H, singlet);
 6.23 (1H, singlet);
 6.72 (1H, doublet, $J = 1.95$ Hz);
 6.78 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 50 6.86 (1H, doublet, $J = 8.30$ Hz);
 7.23 (2H, doublet of multiplets, $J = 8.79$ Hz);
 7.31 (2H, doublet of multiplets, $J = 8.79$ Hz).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 2400 - 3600 (broad), 1690, 1605, 1585, 1515, 1490, 1465, 1415, 1255, 1135.
 55 Mass Spectrum (m/z):
 318 (M^+), 303, 243.

PREPARATION 245 Ethyl (Z)-3-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylate

Prepared as an oil in a yield of 13%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

- 1.11 (3H, triplet, J = 7 Hz);
 10 3.83 (3H, singlet);
 3.88 (3H, singlet);
 4.06 (2H, quartet, J = 7 Hz);
 6.35 (1H, singlet);
 6.75 - 7.00 (3H, multiplet);
 15 7.00 - 7.50 (4H, multiplet).

PREPARATION 25

20

Ethyl (E)-3-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylate

25 Prepared as an oil in a yield of 20%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

- 1.15 (3H, triplet, J = 7 Hz);
 3.81 (3H, singlet);
 3.90 (3H, singlet);
 30 4.08 (2H, quartet, J = 7 Hz);
 6.29 (1H, singlet);
 6.70 - 7.00 (3H, multiplet);
 7.10 - 7.45 (4H, multiplet).

35

PREPARATION 26

40

(Z)-3-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid

Prepared as crystals, melting at 178 - 181 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 90%.

45 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 3.83 (3H, singlet);
 3.89 (3H, singlet);
 6.30 (1H, singlet);
 6.75 (1H, doublet of doublets, J = 8.30 & 1.95 Hz);
 50 6.80 (1H, doublet, J = 8.30 Hz);
 6.85 (1H, doublet, J = 1.95 Hz);
 7.10 (1H, doublet of triplets, J = 7.81 & 1.46 Hz);
 7.20 (1H, triplet, J = 1.46 Hz);
 7.31 (1H, triplet, J = 7.81 Hz);
 55 7.36 (1H, doublet of triplets, J = 7.81 & 1.46 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1690, 1600, 1590, 1580, 1510, 1460, 1420, 1255, 1140. Mass Spectrum (m/z):
 318 (M⁺, ³⁵Cl), 303.

PREPARATION 275 (Z)-3-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acrylic acid

Prepared as crystals, melting at 158 - 160 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 91%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 10 3.81 (3H, singlet);
 3.92 (3H, singlet);
 6.23 (1H, singlet);
 6.73 (1H, doublet, J = 1.95 Hz);
 6.78 (1H, doublet of doublets, J = 8.30 & 1.95 Hz);
 15 6.87 (1H, doublet, J = 8.30 Hz);
 7.15 - 7.40 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1690, 1600, 1580, 1565, 1515, 1460, 1420, 1255, 1135.

Mass Spectrum (m/z):

- 20 318 (M⁺, ³⁵Cl), 303.

PREPARATION 28

25

Ethyl (E)-3-(4-Chlorophenyl)-3-(2,3-dimethoxyphenyl)acrylate

Prepared as crystals, melting at 82 - 84 °C (after recrystallisation from hexane), in a yield of 4%.

30 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.17 (3H, triplet, J = 7.32 Hz);
 3.39 (3H, singlet);
 3.84 (3H, singlet);
 4.10 (2H, quartet, J = 7.32 Hz);
 35 6.16 (1H, singlet);
 6.82 (1H, doublet of doublets, J = 8.30 & 1.46 Hz);
 6.93 (1H, doublet of doublets, J = 8.30 & 1.46 Hz);
 7.04 (1H, triplet, J = 8.30 Hz);
 7.20 (2H, doublet of multiplets, J = 8.79 Hz);
 40 7.29 (2H, doublet of multiplets, J = 8.79 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1715, 1620, 1600, 1580, 1495, 1475, 1430, 1370, 1260, 1170.

Mass Spectrum (m/z):

346 (M⁺, ³⁵Cl), 315, 301, 287.

45

PREPARATION 29

50

Ethyl (Z)-3-(4-Chlorophenyl)-3-(2,3-dimethoxyphenyl)acrylate

Prepared as crystals, melting at 90 - 92 °C (after recrystallisation from hexane), in a yield of 37%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 55 1.11 (3H, triplet, J = 7.32 Hz);
 3.58 (3H, singlet);
 3.89 (3H, singlet);
 4.04 (2H, quartet, J = 7.32 Hz);

6.43 (1H, singlet);
 6.69 (1H, doublet of doublets, $J = 8.30$ & 1.47 Hz);
 6.95 (1H, doublet of doublets, $J = 8.30$ & 1.47 Hz);
 7.08 (1H, triplet, $J = 8.30$ Hz);
 5 7.28 (4H, singlet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1720, 1625, 1590, 1580, 1495, 1480, 1430, 1370, 1260, 1170.
 Mass Spectrum (m/z):
 346 (M^+ , ^{35}Cl), 315, 301, 287.

10

PREPARATION 30

15

(E)-3-(4-Chlorophenyl)-3-(2,3-dimethoxyphenyl)acrylic acid

Prepared as crystals, melting at $129 - 131^\circ \text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 98%.

20 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

3.39 (3H, singlet);
 3.84 (3H, singlet);
 6.16 (1H, singlet);
 6.79 (1H, doublet of doublets, $J = 8.30$ & 1.47 Hz);
 25 6.93 (1H, doublet of doublets, $J = 8.30$ & 1.47 Hz);
 7.04 (1H, triplet, $J = 8.30$ Hz);
 7.20 (1H, doublet of multiplets, $J = 8.79$ Hz);
 7.28 (2H, doublet of multiplets, $J = 8.79$ Hz).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

30 2400 - 3600 (broad), 1690, 1620, 1600, 1580, 1495, 1475, 1425, 1260.

Mass Spectrum (m/z):

318 (M^+ , ^{35}Cl), 287.

35

PREPARATION 31(Z)-3-(4-Chlorophenyl)-3-(2,3-dimethoxyphenyl)acrylic acid

40

Prepared as crystals, melting at 147°C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 98%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

3.57 (3H, singlet);
 45 3.88 (3H, singlet);
 6.38 (1H, singlet);
 6.67 (1H, doublet of doublets, $J = 7.81$ & 1.46 Hz);
 6.94 (1H, doublet of doublets, $J = 7.81$ & 1.46 Hz);
 7.06 (1H, triplet, $J = 7.81$ Hz);
 50 7.20 - 7.33 (4H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1695, 1620, 1590, 1580, 1495, 1480, 1425, 1265.

Mass Spectrum (m/z):

318 (M^+ , ^{35}Cl), 287.

55

PREPARATION 32

Ethyl (Z)-3-(4-Chlorophenyl)-3-(4-isobutoxyphenyl)acrylate

Prepared as an oil in a yield of 13%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 5 1.02 (6H, doublet, J = 6.83 Hz);
 1.14 (3H, triplet, J = 7.32 Hz);
 2.00 - 2.15 (1H, multiplet);
 3.72 (2H, doublet, J = 6.35 Hz);
 4.05 (2H, quartet, J = 7.32 Hz);
 10 6.30 (1H, singlet);
 6.83 (2H, doublet of multiplets, J = 8.79 Hz);
 7.14 (2H, doublet of multiplets, J = 8.79 Hz);
 7.20 (2H, doublet of multiplets, J = 8.79 Hz);
 7.35 (2H, doublet of multiplets, J = 8.79 Hz).
 15 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 1710, 1605, 1515, 1495, 1475, 1375, 1280, 1255, 1170.
 Mass Spectrum (m/z):
 358 (M⁺, ³⁵C1), 313, 302.

20

PREPARATION 3325 Ethyl (E)-3-(4-Chlorophenyl)-3-(4-isobutoxyphenyl)acrylate

Prepared as an oil in a yield of 16%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 30 1.03 (6H, doublet, J = 6.83 Hz);
 1.17 (3H, triplet, J = 7.32 Hz);
 2.00 - 2.20 (1H, multiplet);
 3.74 (2H, doublet, J = 6.35 Hz);
 4.09 (2H, quartet, J = 7.32 Hz);
 6.23 (1H, singlet);
 35 6.89 (2H, doublet of multiplets, J = 9.28 Hz);
 7.11 (2H, doublet of multiplets, J = 9.28 Hz);
 7.22 (2H, doublet of multiplets, J = 8.79 Hz);
 7.29 (2H, doublet of multiplets, J = 8.79 Hz).
 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 40 1710, 1605, 1590, 1510, 1490, 1470, 1370, 1285, 1160.
 Mass Spectrum (m/z):
 358 (M⁺, ³⁵C1), 313, 302.

45

PREPARATION 34(Z)-3-(4-Chlorophenyl)-3-(4-isobutoxyphenyl)acrylic acid

50

Prepared as crystals, melting at 172 - 174 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 80%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 55 1.02 (6H, doublet, J = 6.83 Hz);
 1.95 - 2.20 (1H, multiplet);
 3.72 (2H, doublet, J = 6.84 Hz);
 6.27 (1H, singlet);
 6.83 (2H, doublet of multiplets, J = 8.30 Hz)

7.13 (2H, doublet of multiplets, $J = 8.30$ Hz);

7.18 (2H, doublet of multiplets, $J = 8.79$ Hz);

7.34 (2H, doublet of multiplets, $J = 8.79$ Hz).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

5 2400 - 3600 (broad), 1695, 1600, 1590, 1510, 1295, 1250, 1175.

Mass Spectrum (m/z):

330 (M^+ , ^{35}Cl), 274, 257.

10

PREPARATION 35

(E)-3-(4-Chlorophenyl)-3-(4-isobutoxyphenyl)acrylic acid

15

Prepared as crystals, melting at $150 - 152^\circ \text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 100%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.04 (6H, doublet, $J = 6.35$ Hz);

20 2.00 - 2.20 (1H, multiplet);

3.75 (2H, doublet, $J = 6.34$ Hz);

6.19 (1H, singlet);

6.87 (2H, doublet of multiplets, $J = 8.79$ Hz);

7.12 (2H, doublet of multiplets, $J = 8.79$ Hz);

25 7.21 (2H, doublet of multiplets, $J = 8.78$ Hz);

7.30 (2H, doublet of multiplets, $J = 8.78$ Hz).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1690, 1610, 1590, 1515, 1290, 1245, 1175.

Mass Spectrum (m/z):

30 330 (M^+ , ^{35}Cl), 274, 257.

PREPARATION 36

35

Ethyl (Z)-3-(4-Chlorophenyl)-3-(4-propoxyphenyl)acrylate

Prepared as an oil in a yield of 19%.

40 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.03 (3H, triplet, $J = 7.32$ Hz);

1.14 (3H, triplet, $J = 7.33$ Hz);

1.74 - 1.90 (2H, multiplet);

3.92 (2H, triplet, $J = 6.83$ Hz);

45 4.05 (2H, quartet, $J = 7.33$ Hz);

6.31 (1H, singlet);

6.83 (2H, doublet of multiplets, $J = 9.28$ Hz);

7.14 (1H, doublet of multiplets, $J = 8.79$ Hz);

7.20 (2H, doublet of multiplets, $J = 9.28$ Hz);

50 7.36 (2H, doublet of multiplets, $J = 8.79$ Hz).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1705, 1600, 1595, 1510, 1370, 1275, 1250, 1160, 1150.

Mass Spectrum (m/z):

344 (M^+ , ^{35}Cl), 302, 299, 272, 257, 230.

55

PREPARATION 37

Ethyl (E)-3-(4-Chlorophenyl)-3-(4-propoxyphenyl)acrylate

Prepared as an oil in a yield of 27%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 5 1.05 (3H, triplet, J = 7.33 Hz);
 1.16 (3H, triplet, J = 7.33 Hz);
 1.75 - 1.95 (2H, multiplet);
 3.95 (2H, triplet, J = 6.84 Hz);
 4.09 (2H, quartet, J = 7.33 Hz);
 10 6.23 (1H, singlet);
 6.89 (2H, doublet of multiplets, J = 8.78 Hz);
 7.12 (2H, doublet of multiplets, J = 8.78 Hz);
 7.22 (2H, doublet of multiplets, J = 8.79 Hz);
 7.29 (2H, doublet of multiplets, J = 8.79 Hz).
 15 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 1710, 1610, 1590, 1510, 1490, 1370, 1290, 1240, 1170, 1150.
 Mass Spectrum (m/z):
 344 (M⁺, ³⁵Cl), 302, 299, 272, 257, 230.

20

PREPARATION 3825 (Z)-3-(4-Chlorophenyl)-3-(4-propoxyphenyl)acrylic acid

Prepared as crystals, melting at 159 - 161 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 96%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 30 1.03 (3H, triplet, J = 7.32 Hz);
 1.70 - 1.90 (2H, multiplet);
 3.93 (2H, triplet, J = 6.84 Hz);
 6.27 (1H, singlet);
 6.83 (2H, doublet of multiplets, J = 8.79 Hz);
 35 7.14 (2H, doublet of multiplets, J = 8.30 Hz);
 7.19 (2H, doublet of multiplets, J = 8.79 Hz);
 7.34 (2H, doublet of multiplets, J = 8.30 Hz).
 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 2400 - 3600 (broad), 1695, 1600, 1595, 1510, 1280, 1255, 1180.
 40 Mass Spectrum (m/z):
 316 (M⁺, ³⁵Cl), 274, 257, 229.

PREPARATION 39

45

(E)-3-(4-Chlorophenyl)-3-(4-propoxyphenyl)acrylic acid

- 50 Prepared as crystals, melting at 145 - 147 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 97%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.06 (3H, triplet, J = 7.33 Hz);
 1.75 - 1.90 (2H, multiplet);
 55 3.95 (3H, triplet, J = 6.35 Hz);
 6.19 (1H, singlet);
 6.88 (2H, doublet of multiplets, J = 8.79 Hz);
 7.13 (2H, doublet of multiplets, J = 8.79 Hz);

EP 0 395 446 A2

7.21 (2H, doublet of multiplets, $J = 8.79$ Hz)
7.30 (2H, doublet of multiplets, $J = 8.79$ Hz).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
2400 - 3600 (broad), 1690, 1610, 1590, 1510, 1495, 1290, 1270, 1250, 1175.
5 Mass Spectrum (m/z):
316 (M^+ , ^{35}Cl), 274, 257, 229.

PREPARATION 40

10

Ethyl (E)-3-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl) acrylate

15 Prepared as crystals, melting at $133 - 135^\circ \text{C}$ (after recrystallisation from diethyl ether), in a yield of 22%.
Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
1.15 (3H, triplet, $J = 7.32$ Hz);
3.78 (6H, singlet);
20 3.87 (3H, singlet);
4.07 (2H, quartet, $J = 7.32$ Hz);
6.31 (1H, singlet);
6.48 (2H, singlet);
7.03 - 7.13 (2H, multiplet);
25 7.17 - 7.25 (2H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1710, 1605, 1580, 1505, 1465, 1415, 1355, 1165, 1155, 1130.
Mass Spectrum (m/z):
360 (M^+), 345, 315.

30

PREPARATION 41

35

Ethyl (Z)-3-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl) acrylate

Prepared as crystals, melting at $62 - 64^\circ \text{C}$ (after recrystallisation from a mixture of diethyl ether and hexane), in a yield of 37%.
40 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
1.14 (3H, triplet, $J = 7.33$ Hz);
3.80 (6H, singlet);
3.90 (3H, singlet);
4.08 (2H, quartet, $J = 7.33$ Hz);
45 6.26 (1H, singlet);
6.41 (2H, singlet);
6.98 - 7.08 (2H, multiplet);
7.27 - 7.36 (2H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
50 1710, 1600, 1585, 1505, 1465, 1415, 1370, 1310, 1160, 1130.
Mass Spectrum (m/z):
360 (M^+), 345, 315.

55

PREPARATION 42

(E)-3-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid

Prepared as crystals, melting at 201 - 204 °C (after recrystallisation from a mixture of methylene chloride, diethyl ether and hexane), in a yield of 98%.

5 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

3.78 (6H, singlet);

3.87 (3H, singlet);

6.28 (1H, singlet);

6.46 (2H, singlet);

10 7.02 - 7.12 (2H, multiplet);

7.12 - 7.25 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1690, 1600, 1580, 1505, 1130.

Mass Spectrum (m/z):

15 332 (M⁺), 317.

PREPARATION 43

20

(Z)-3-(4-Fluorophenyl)-3-(3,4,5-trimethoxyphenyl)acrylic acid

Prepared as crystals, melting at 187 - 189 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 100%.

25 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

3.79 (6H, singlet);

3.91 (3H, singlet);

6.24 (1H, singlet);

30 6.42 (2H, singlet);

6.99 - 7.09 (2H, multiplet);

7.27 - 7.35 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1690, 1600, 1585, 1505, 1415, 1125.

35 Mass Spectrum (m/z):

332 (M⁺), 317.

PREPARATION 44

40

Ethyl (E)-3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acrylate

45 Prepared as an oil in a yield of 20%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1.16 (3H, triplet J = 7.32 Hz);

3.83 (3H, singlet);

3.85 (3H, singlet);

50 3.89 (3H, singlet);

4.08 (2H, quartet, J = 7.32 Hz);

6.23 (1H, singlet);

6.77 - 6.89 (3H, multiplet);

6.91 (2H, doublet of multiplets, J = 8.78 Hz);

55 7.16 (2H, doublet of multiplets, J = 8.78 Hz). Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1705, 1605, 1580, 1510, 1465, 1290, 1165, 1135. Mass Spectrum (m/z):

342 (M⁺), 313, 297.

PREPARATION 455 Ethyl (Z)-3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acrylate

Prepared as an oil in a yield of 30%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.15 (3H, triplet J = 7.32 Hz);
 10 3.81 (3H, singlet);
 3.85 (3H, singlet);
 3.92 (3H, singlet);
 4.07 (2H, quartet, J = 7.32 Hz);
 6.24 (1H, singlet);
 15 6.71 (1H, doublet, J = 1.95 Hz);
 6.77 - 6.94 (4H, multiplet);
 7.26 (2H, doublet of multiplets, J = 8.79 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1705, 1600, 1510, 1465, 1250, 1170, 1135.

20 Mass Spectrum (m/z):

342 (M⁺), 313, 297.

PREPARATION 46

25

(E)-3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid

30 Prepared as crystals, melting at 161 - 163 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 91%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 3.82 (3H, singlet);
 3.85 (3H, singlet);
 35 3.89 (3H, singlet);
 6.20 (1H, singlet);
 6.74 - 6.82 (2H, multiplet);
 6.84 (1H, broad singlet);
 6.89 (2H, doublet of multiplets, J = 8.79 Hz);
 40 7.17 (2H, doublet of multiplets, J = 8.79 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1685, 1605, 1595, 1515, 1465, 1290, 1245, 1170, 1135.

Mass Spectrum (m/z):

314 (M⁺), 299.

45

PREPARATION 47

50

(Z)-3-(3,4-Dimethoxyphenyl)-3-(4-methoxyphenyl)acrylic acid

Prepared as crystals, melting at 149 - 152 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 97%.

55 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 3.81 (3H, singlet);
 3.83 (3H, singlet);
 3.92 (3H, singlet);

6.21 (1H, singlet);
 6.74 (1H, doublet, $J = 1.95$ Hz);
 6.80 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 6.82 - 6.93 (3H, multiplet);
 7.14 - 7.29 (2H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 2400 - 3600 (broad), 1690, 1600, 1515, 1465, 1255, 1175, 1135.
 Mass Spectrum (m/z):
 314(M^+), 299, 270.

PREPARATION 48

Ethyl (Z)-3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acrylate

Prepared as an oil in a yield of 62%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 60 MHz) δ ppm:

1.15 (3H, triplet, $J = 7$ Hz);
 3.80 (3H, singlet);
 4.06 (2H, quartet $J = 7$ Hz);
 6.35 (1H, singlet);
 6.8 - 7.4 (7H, multiplet).

PREPARATION 49

Ethyl (E)-3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acrylate

Prepared as an oil in a yield of 23%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 60 MHz) δ ppm:

1.16 (3H, triplet, $J = 7$ Hz);
 3.84 (3H, singlet);
 4.06 (2H, quartet $J = 7$ Hz);
 6.23 (1H, singlet);
 6.7 - 7.5 (7H, multiplet).

PREPARATION 50

(Z)-3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acrylic acid

Prepared as crystals, melting at $181 - 184^\circ \text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 84%.

Nuclear Magnetic Resonance Spectrum (CD_3OD , 270 MHz) δ ppm:

3.80 (3H, singlet);
 6.36 (1H, singlet);
 6.91 (2H, doublet of multiplets, $J = 9.28$ Hz);
 7.08 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
 7.23 (2H, doublet of multiplets, $J = 9.28$ Hz);
 7.31 (1H, doublet, $J = 1.95$ Hz);

7.51 (1H, doublet, $J = 8.30$ Hz).

Infrared Absorption Spectrum (KBr) ν_{\max} cm^{-1} :

2300 - 3400 (broad), 1692, 1597, 1585, 1510, 1288, 1254, 1214, 1178, 1162.

Mass Spectrum (m/z):

5 322 (M^+ , ^{35}Cl), 305, 277.

PREPARATION 51

10

(E)-3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acrylic acid

Prepared as crystals, melting at $193 - 196^\circ\text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 95%.

15 Nuclear Magnetic Resonance Spectrum (CD_3OD , 270 MHz) δ ppm:

3.83 (3H, singlet);

6.30 (1H, singlet);

6.93 (2H, doublet of multiplets, $J = 8.79$ Hz);

20 7.12 (2H, doublet of multiplets, $J = 8.79$ Hz);

7.23 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);

7.38 (1H, doublet, $J = 1.95$ Hz);

7.50 (1H, doublet, $J = 8.30$ Hz).

Infrared Absorption Spectrum (KBr) ν_{\max} cm^{-1} :

25 2300 - 3400 (broad), 1688, 1662, 1602, 1512, 1407, 1281, 1253, 1207, 1177.

Mass Spectrum (m/z):

322 (M^+ , ^{35}Cl), 305, 277.

30

PREPARATION 52

Ethyl (E)-3-(3,4-Dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acrylate

35

Prepared as crystals, melting at $72 - 74^\circ\text{C}$ (after recrystallisation from hexane), in a yield of 13%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.08 (3H, triplet, $J = 7.32$ Hz);

3.84 (3H, singlet);

40 3.89 (3H, singlet);

4.03 (2H, quartet, $J = 7.32$ Hz);

6.37 (1H, singlet);

6.72 (1H, doublet of doublets, $J = 8.30$ & 1.96 Hz);

6.80 (1H, doublet, $J = 8.30$ Hz);

45 6.87 (1H, doublet, $J = 1.96$ Hz);

7.35 - 7.70 (4H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{\max} cm^{-1} :

1710, 1595, 1515, 1460, 1370.

Mass Spectrum (m/z):

50 380(M^+), 361, 335.

PREPARATION 53

55

Ethyl (Z)-3-(3,4-Dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acrylate

EP 0 395 446 A2

Prepared as an oil in a yield of 16%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1. 18 (3H, triplet, $J = 7.32$ Hz);
3.82 (3H, singlet);
5 3.93 (3H, singlet);
4.11 (2H, quartet, $J = 7.32$ Hz);
6.30 (1H, singlet);
6.71 (1H, doublet, $J = 1.95$ Hz);
6.81 (1H, doublet of doublets, $J = 8.30$ & 1.96 Hz);
10 6.89 (1H, doublet, $J = 8.30$ Hz);
7.40 - 7.50 (2H, multiplet);
7.57 - 7.68 (2H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1710, 1600, 1580, 1515, 1460, 1370, 1325.
15 Mass Spectrum (m/z):
380(M^+), 361, 335.

PREPARATION 54

20

(E)-3-(3,4-Dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acrylic acid

- 25 Prepared as crystals (melting at $142 - 144^\circ\text{C}$, after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 100%.

PREPARATION 55

30

(Z)-3-(3,4-Dimethoxyphenyl)-3-(3-trifluoromethylphenyl)acrylic acid

- 35 Prepared as crystals (melting at $140 - 143^\circ\text{C}$, after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 100%.

PREPARATION 56

40

Ethyl (E)-3-(3,4-Dimethoxyphenyl)-3-(4-methylphenyl)acrylate

- 45 Prepared as crystals, melting at $75 - 77^\circ\text{C}$ (after recrystallisation from hexane), in a yield of 21%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.14 (3H, triplet, $J = 7.32$ Hz);
2.39 (3H, singlet);
3.83 (3H, singlet);
50 3.88 (3H, singlet);
4.06 (2H, quartet, $J = 7.32$ Hz);
6.27 (1H, singlet);
6.77 (1H, doublet, $J = 8.30$ Hz);
6.81 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);
55 6.89 (1H, doublet, $J = 1.95$ Hz);
7.01 - 7.22 (4H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1705, 1600, 1580, 1510, 1465, 1440, 1370, 1290, 1250, 1160, 1130.

Mass Spectrum (m/z):
326 (M⁺), 297, 281, 254.

5

PREPARATION 57Ethyl (Z)-3-(3,4-Dimethoxyphenyl)-3-(4-methylphenyl)acrylate

10

Prepared as crystals (melting at 69 - 70 °C after recrystallisation from hexane), in a yield of 38%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1.16 (3H, triplet, J = 7.32 Hz);

2.36 (3H, singlet);

15 3.81 (3H, singlet);

3.91 (3H, singlet);

4.08 (2H, quartet, J = 7.32 Hz);

6.27 (1H, singlet);

6.72 (1H, doublet, J = 1.95 Hz);

20 6.81 (1H, doublet of doublets, J = 7.81 & 1.95 Hz);

6.88 (1H, doublet, J = 7.81 Hz).

7.13 (2H, doublet of multiplets, J = 8.30 Hz);

7.21 (2H, doublet of multiplets, J = 8.30 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

25 1710, 1600, 1580, 1510, 1465, 1415, 1370, 1250, 1160, 1135.

Mass Spectrum (m/z):

326 (M⁺), 297, 281, 254.

30

PREPARATION 58(E)-3-(3,4-Dimethoxyphenyl)-3-(4-methylphenyl)acrylic acid

35

Prepared as crystals, melting at 167 - 170 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 97%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.39 (3H, singlet);

40 3.88 (3H, singlet);

3.92 (3H, singlet);

6.24 (1H, singlet);

7.79 (1H, multiplet);

6.86 (1H, broad singlet);

45 7.08 - 7.22 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

2400 - 3600 (broad), 1690, 1600, 1580, 1510, 1465, 1440, 1420, 1325, 1290, 1250, 1175, 1135.

Mass Spectrum (m/z):

298(M⁺), 283.

50

PREPARATION 59

55

(Z)-3-(3,4-Dimethoxyphenyl)-3-(4-methylphenyl)acrylic acid

Prepared as crystals, melting at 185 - 188 °C (after recrystallisation from a mixture of methylene

EP 0 395 446 A2

chlorid and hexane), in a yield of 96%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

2.36 (3H, singlet);

3.80 (3H, singlet);

5 3.92 (3H, singlet);

6.24 (1H, singlet);

6.75 (1H, doublet, $J = 1.95$ Hz);

6.79 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);

6.86 (1H, doublet, $J = 8.30$ Hz);

10 7.10 - 7.23 (4H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1690, 1605, 1515, 1465, 1420, 1260, 1180, 1140.

Mass Spectrum (m/z):

298 (M^+), 283.

15

PREPARATION 60

20

Ethyl (Z)-3-(3,4-Dichlorophenyl)-3-(3-methylphenyl)acrylate

Prepared as an oil in a yield of 52%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

25 1.17 (3H, triplet, $J = 7.32$ Hz);

2.33 (3H, singlet);

4.08 (2H, quartet, $J = 7.32$ Hz);

6.36 (1H, singlet);

7.03 - 7.13 (3H, multiplet);

30 7.15 - 7.23 (2H, multiplet);

7.30 (1H, doublet, $J = 1.95$ Hz);

7.46 (1H, doublet, $J = 8.30$ Hz).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1715, 1620, 1470, 1370, 1280, 1170, 1150.

35 Mass Spectrum (m/z):

334 (M^+ , ^{35}Cl), 305, 289, 262.

PREPARATION 61

40

Ethyl (E)-3-(3,4-Dichlorophenyl)-3-(3-methylphenyl)acrylate

45 Prepared as an oil in a yield of 19%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.11 (3H, triplet, $J = 7.32$ Hz);

2.35 (3H, singlet);

4.05 (2H, quartet, $J = 7.32$ Hz);

50 6.30 (1H, singlet);

6.95 - 7.05 (2H, multiplet);

7.12 (1H, doublet of doublets, $J = 8.79$ & 1.95 Hz);

7.15 - 7.32 (2H, multiplet);

7.379 (1H, doublet, $J = 1.95$ Hz);

55 7.385 (1H, doublet, $J = 8.79$ Hz).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

1720, 1620, 1470, 1380, 1370, 1350, 1280, 1250, 1175.

Mass Spectrum (m/z):

334 (M^+ , ^{35}Cl), 305, 289, 262.

PREPARATION 62

5

(Z)-3-(3,4-Dichlorophenyl)-3-(3-methylphenyl)acrylic acid

10 Prepared as crystals, melting at 163 - 165 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 95%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.33 (3H, singlet);

6.33 (1H, singlet);

15 7.00 - 7.10 (3H, multiplet);

7.18 - 7.28 (2H, multiplet);

7.29 (1H, doublet, $J = 1.95$ Hz);

7.45 (1H, doublet, $J = 7.81$ Hz).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

20 2400 - 3600 (broad), 1695, 1600, 1585, 1475, 1290, 1125.

Mass Spectrum (m/z):

306 (M^+ , ^{35}Cl), 291, 261.

25

PREPARATION 63

(E)-3-(3,4-Dichlorophenyl)-3-(3-methylphenyl)acrylic acid

30

Prepared as crystals, melting at 152 - 154 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 92%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

2.34 (3H, singlet);

35 6.26 (1H, singlet);

6.94 - 7.03 (2H, multiplet);

7.09 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);

7.18 - 7.32 (2H, multiplet);

7.35 (1H, doublet, $J = 1.96$ Hz);

40 7.39 (1H, doublet, $J = 8.30$ Hz).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1695, 1620, 1470, 1410, 1285, 1180, 1130.

Mass Spectrum (m/z):

306 (M^+ , ^{35}Cl), 291, 261.

45

PREPARATION 64

50

Ethyl (E)-3-(3,4-Dimethoxyphenyl)-3-(3-methylphenyl)acrylate

Prepared as an oil in a yield of 23%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

55 1.11 (3H, triplet, $J = 7.32$ Hz);

2.36 (3H, singlet);

3.83 (3H, singlet);

3.88 (3H, singlet);

- 4.04 (2H, quartet, $J = 7.32$ Hz);
 6.29 (1H, singlet);
 6.75 - 6.84 (2H, multiplet);
 6.90 (1H, broad singlet);
 5 6.94 - 7.05 (2H, multiplet);
 7.15 - 7.31 (2H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1710, 1600, 1580, 1515, 1470, 1445, 1330, 1295, 1255, 1160, 1145, 1130.
 Mass Spectrum (m/z):
 10 326 (M^+), 297, 281, 254.

PREPARATION 65

15

Ethyl (Z)-3-(3,4-Dimethoxyphenyl)-3-(3-methylphenyl)acrylate

Prepared as an oil in a yield of 33%.

- 20 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 1.16 (3H, triplet, $J = 7.33$ Hz);
 2.33 (3H, singlet);
 3.81 (3H, singlet);
 3.92 (3H, singlet);
 25 4.08 (2H, quartet, $J = 7.32$ Hz);
 6.72 (1H, doublet, $J = 1.96$ Hz);
 6.81 (1H, doublet of doublets, $J = 8.30$ & 1.96 Hz);
 6.88 (1H, doublet, $J = 8.30$ Hz);
 7.07 - 7.26 (4H, multiplet).
 30 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 1715, 1610, 1590, 1520, 1470, 1260, 1180, 1160, 1145, 1135.
 Mass Spectrum (m/z):
 326 (M^+), 297, 281, 254.

35

PREPARATION 66

(E)-3-(3,4-Dimethoxyphenyl)-3-(3-methylphenyl)acrylic acid

Prepared as crystals, melting at $140 - 143^\circ \text{C}$ (after recrystallisation from a mixture of diethyl ether and hexane), in a yield of 95%.

- Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
 45 2.35 (3H, singlet);
 3.82 (3H, singlet);
 3.89 (3H, singlet);
 6.27 (1H, singlet);
 6.74 - 6.83 (2H, multiplet);
 50 6.87 (1H, broad singlet);
 6.99 - 7.06 (2H, multiplet);
 7.15 - 7.31 (2H, multiplet).
 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
 2400 - 3600 (broad), 1695, 1600, 1580, 1515, 1470, 1260, 1170, 1145, 1130.
 55 Mass Spectrum (m/z):
 298 (M^+), 283, 253.

PREPARATION 675 (Z)-3-(3,4-Dimethoxyphenyl)-3-(3-methylphenyl)acrylic acid

Prepared as crystals, melting at 148 - 150 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 96%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 10 2.33 (3H, singlet);
 3.81 (3H, singlet);
 3.92 (3H, singlet);
 6.24 (2H, singlet);
 6.75 (1H, doublet, J = 1.96 Hz);
 15 6.80 (1H, doublet of doublets, J = 8.30 & 1.96 Hz);
 6.87 (1H, doublet, J = 8.30 Hz);
 7.05 - 7.14 (2H, multiplet);
 7.16 - 7.24 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

- 20 2400 - 3600 (broad), 1690, 1605, 1585, 1515, 1450, 1440, 1420, 1255, 1175, 1135.
 Mass Spectrum (m/z):
 298 (M⁺), 283, 253.

25

PREPARATION 6830 Ethyl (Z)-3-(2-Chlorophenyl)-3-(4-methoxyphenyl)acrylate

Prepared as an oil in a yield of 81%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1. 10 (3H, triplet, J = 7.33 Hz);
 3.81 (3H, singlet);
 35 4.03 (2H, quartet, J = 7.33 Hz);
 6.48 (1H, singlet);
 6.85 (2H, doublet of multiplets, J = 9.28 Hz);
 7.11 - 7.20 (1H, multiplet);
 7.26 (2H, doublet of multiplets, J = 9.28 Hz);
 40 7.26 - 7.37 (2H, multiplet);
 7.40 - 7.50 (1H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

- 1710, 1605, 1590, 1575, 1515, 1465, 1370, 1355, 1280, 1255, 1160.
 Mass Spectrum (m/z):
 45 316 (M⁺, ³⁵Cl), 281, 271, 253.

PREPARATION 69

50

(Z)-3-(2-Chlorophenyl)-3-(4-methoxyphenyl)acrylic acid

55 Prepared as crystals, melting at 162 - 164 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 85%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 3.80 (3H, singlet);
 6.44 (1H, singlet);

EP 0 395 446 A2

- 6.84 (2H, doublet of multiplets, $J = 8.79$ Hz);
7.09 - 7.16 (1H, multiplet);
7.24 (2H, doublet of multiplets, $J = 8.79$ Hz);
7.26 - 7.35 (2H, multiplet);
5 7.37 - 7.46 (1H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
2400 - 3600 (broad), 1700, 1620, 1605, 1595, 1575, 1515, 1425, 1290, 1260, 1180, 1160. Mass Spectrum
(m/z):
288 (M^+ , ^{35}Cl), 253, 238.

10

PREPARATION 70

15

Ethyl (Z)-3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acrylate

- Prepared as an oil in a yield of 8%.
Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
20 1.13 (3H, triplet, $J = 7.32$ Hz);
3.78 (3H, singlet);
4.06 (2H, quartet, $J = 7.32$ Hz);
6.37 (1H, singlet);
6.81 (1H, triplets, $J = 1.96$ Hz);
25 6.86 (1H, doubled doublet of doublets, $J = 8.31, 1.96$ & 0.98 Hz);
6.91 (1H, doubled doublet of doublets, $J = 8.31, 1.96$ & 0.98 Hz);
7.10 (1H, doublet of triplets, $J = 7.81$ & 1.95 Hz);
7.20 (1H, triplet, $J = 1.95$ Hz);
7.25 (1H, triplet, $J = 7.81$ Hz);
30 7.31 (1H, triplet, $J = 7.81$ Hz);
7.35 (1H, doublet of triplets, $J = 7.81$ & 1.95 Hz).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1715, 1620, 1600, 1580, 1490, 1470, 1435, 1370, 1350, 1290, 1280, 1170.
Mass Spectrum (m/z):
35 316 (M^+ , ^{35}Cl), 287, 271, 243, 228.

PREPARATION 71

40

Ethyl (E)-3-(3-Chlorophenyl)-3-(3-methoxyphenyl) acrylate

- Prepared as an oil in a yield of 18%.
45 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:
1.12 (3H, triplet, $J = 7.32$ Hz);
3.79 (3H, singlet);
4.06 (2H, quartet, $J = 7.32$ Hz);
6.33 (1H, singlet);
50 6.72 (1H, doublet of doublets, $J = 2.44$ & 1.46 Hz);
6.79 (1H, doublet of triplets, $J = 7.81$ & 1.46 Hz);
6.93 (1H, doubled doublet of doublets, $J = 8.30, 2.44$ & 1.46 Hz);
7.18 (1H, doublet of triplets, $J = 7.32$ & 1.46 Hz);
7.22 - 7.36 (4H, multiplet).
55 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1720, 1620, 1590, 1580, 1570, 1490, 1470, 1430, 1370, 1350, 1290, 1260, 1170.
Mass Spectrum (m/z):
316 (M^+ , ^{35}Cl), 287, 271, 243, 228.

PREPARATION 725 (Z)-3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acrylic acid

Prepared as crystals, melting at 115 - 117° C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 98%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 10 3.78 (3H, singlet);
 6.35 (1H, singlet);
 6.78 (1H, triplet, J = 1.47 Hz);
 6.84 (1H, doublet of multiplets, J = 7.81 Hz);
 6.93 (1H, doublet of multiplets, J = 7.81 Hz);
 15 7.10 (1H, doublet of triplets, J = 7.32 & 1.47 Hz);
 7.25 (1H, triplet, J = 7.81 Hz);
 7.30 (1H, triplet, J = 7.32 Hz);
 7.36 (1H, doublet of triplets, J = 7.33 & 1.47 Hz);
 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 20 2400 - 3600 (broad), 1695, 1620, 1600, 1580, 1490, 1435, 1410, 1345, 1290, 1150.
 Mass Spectrum (m/z):
 288 (M⁺, ³⁵Cl), 271, 243.

25

PREPARATION 7330 (E)-3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acrylic acid

Prepared as crystals, melting at 140 - 142° C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 96%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 3.79 (3H, singlet);
 35 6.30 (1H, singlet);
 6.72 (1H, doublet of doublets, J = 2.44 & 1.47 Hz);
 6.78 (1H, doublet of multiplets, J = 7.32 Hz);
 6.93 (1H, doubled doublet of doublets, J = 8.30, 2.44 & 0.97 Hz);
 7.16 (1H, doublet of triplets, J = 7.81 & 1.47 Hz);
 40 7.23 - 7.38 (4H, multiplet).
 Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:
 2400 - 3600 (broad), 1695, 1620, 1600, 1590, 1570, 1490, 1470, 1460, 1430, 1350, 1285.
 Mass Spectrum (m/z):
 288 (M⁺, ³⁵Cl), 271, 243.

45

PREPARATION 74

50

Ethyl (Z)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylate

Prepared as an oil in a yield of 10%.

55 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.12 (3H, triplet, J = 7.32 Hz);
 3.82 (3H, singlet);
 4.05 (2H, quartet, J = 7.32 Hz);

EP 0 395 446 A2

6.32 (1H, singlet);
6.85 (2H, doublet of multiplets, $J = 9.28$ Hz);
7.09 (1H, doublet of triplets, $J = 7.30$ & 1.96 Hz);
7.18 - 7.39 (5H, multiplet).
5 Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1710, 1605, 1600, 1570, 1515, 1465, 1420, 1370, 1350, 1290, 1275, 1255, 1170, 1155.
Mass Spectrum (m/z):
316 (M^+ , ^{35}Cl), 287, 271, 244, 228.

10

PREPARATION 75

15 Ethyl (E)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylate

Prepared as an oil in a yield of 14%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

1.17 (3H, triplet, $J = 7.32$ Hz);
20 3.84 (3H, singlet);
4.09 (2H, quartet, $J = 7.32$ Hz);
6.25 (1H, singlet);
6.91 (2H, doublet of multiplets, $J = 8.79$ Hz);
7.14 (2H, doublet of multiplets, $J = 8.79$ Hz);
25 7.15 - 7.36 (4H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1715, 1610, 1570, 1515, 1470, 1370, 1355, 1295, 1250, 1175.
Mass Spectrum (m/z):
316 (M^+ , ^{35}Cl), 287, 271, 244, 228.

30

PREPARATION 76

35

(Z)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylic acid

Prepared as crystals, melting at $158 - 160^\circ\text{C}$ (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 94%.

40 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

3.82 (3H, singlet);
6.29 (1H, singlet);
6.85 (2H, doublet of multiplets, $J = 9.28$ Hz);
7.09 (2H, doublet of triplets, $J = 7.30$ & 1.46 Hz);
45 7.16 - 7.38 (5H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
2400 - 3600 (broad), 1695, 1605, 1590, 1570, 1515, 1425, 1285, 1255, 1180.
Mass Spectrum (m/z):
288 (M^+ , ^{35}Cl), 271, 243.

50

PREPARATION 77

55

(E)-3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acrylic acid

Prepared as crystals, melting at $119 - 120^\circ\text{C}$ (after recrystallisation from a mixture of methylene

EP 0 395 446 A2

chlorid and hexane), in a yield of 92%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

3.85 (3H, singlet);

6.21 (1H, singlet);

5 6.90 (2H, doublet of multiplets, J = 8.79 Hz);

7.15 (2H, doublet of multiplets, J = 8.79 Hz);

7.12 - 7.38 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1695, 1610, 1570, 1515, 1420, 1295, 1250, 1180.

10 Mass Spectrum (m/z):

288 (M⁺, ³⁵Cl), 271, 243.

PREPARATION 78

15

Ethyl (Z)-3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acrylate

20 Prepared as an oil, in a yield of 4%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1.03 (3H, triplet, J = 7.32 Hz);

1.16 (3H, triplet, J = 7.32 Hz);

1.70 - 1.90 (2H, multiplet);

25 3.93 (2H, triplet, J = 6.84 Hz);

4.07 (2H, quartet, J = 7.32 Hz);

6.32 (1H, singlet);

6.84 (2H, doublet of multiplets, J = 8.79 Hz);

7.06 (1H, doublet of doublets, J = 8.30 & 1.95 Hz);

30 7.20 (2H, doublet of multiplets, J = 8.79 Hz);

7.29 (1H, doublet, J = 1.95 Hz);

7.45 (1H, doublet, J = 8.30 Hz).

Mass Spectrum (m/z):

378 (M⁺, ³⁵Cl), 336, 333, 308, 305, 291, 264.

35

PREPARATION 79

40

Ethyl (E)-3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acrylate

Prepared as an oil, in a yield of 5%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

45 1.05 (3H, triplet, J = 7.32 Hz);

1.17 (3H, triplet, J = 7.32 Hz);

1.75 - 1.90 (2H, multiplet);

3.95 (2H, triplet, J = 6.35 Hz);

4.09 (2H, quartet, J = 7.32 Hz);

50 6.22 (1H, singlet);

6.90 (2H, doublet of multiplets, J = 8.79 Hz);

7.11 (2H, doublet of multiplets, J = 8.79 Hz);

7.13 (1H, doublet of doublets, J = 8.30 & 1.96 Hz);

7.38 (1H, doublet, J = 1.96 Hz);

55 7.39 (1H, doublet, J = 8.30 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1715, 1630, 1515, 1470, 1390, 1370, 1350, 1290, 1280, 1245, 1170.

Mass Spectrum (m/z):

378 (M^+ , ^{35}Cl), 336, 333, 308, 305, 291, 264.

PREPARATION 80

5

(Z)-3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acrylic acid

10 Prepared as crystals, melting at 161 - 163 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 96%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.03 (3H, triplet, $J = 7.32$ Hz);

1.70 - 1.90 (2H, multiplet);

15 3.93 (2H, triplet, $J = 6.84$ Hz);

6.29 (1H, singlet);

6.85 (2H, doublet of multiplets, $J = 8.79$ Hz);

7.06 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);

7.19 (2H, doublet of multiplets, $J = 8.79$ Hz);

20 7.28 (1H, doublet, $J = 1.95$ Hz);

7.45 (1H, doublet, $J = 8.30$ Hz).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1695, 1605, 1590, 1515, 1475, 1285, 1255, 1180.

Mass Spectrum (m/z):

25 350 (M^+ , ^{35}Cl), 308, 291, 263.

PREPARATION 81

30

(E)-3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acrylic acid

35 Prepared as crystals, melting at 155 - 157 °C (after recrystallisation from a mixture of methylene chloride and hexane), in a yield of 85%.

PREPARATION 82

40

Ethyl (E)-3-(4-ethoxy-3-methoxyphenyl)cinnamate

Prepared as crystals, melting at 89 - 91 °C (after recrystallization from hexane), in a yield of 21%.

45 Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.10 (3H, triplet, $J = 7.32$ Hz);

1.46 (3H, triplet, $J = 7.33$ Hz);

3.81 (3H, singlet);

4.03 (2H, quartet, $J = 7.33$ Hz);

50 4.10 (2H, quartet, $J = 7.33$ Hz);

6.31 (1H, singlet);

6.77 (2H, broad singlet);

6.90 (1H, broad singlet);

7.16 - 7.25 (2H, multiplet);

55 7.32 - 7.41 (3H, multiplet).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

1710, 1615, 1600, 1580, 1515, 1480, 1470, 1370, 1320, 1290, 1250, 1160, 1135.

Mass Spectrum (m/z):

EP 0 395 446 A2

326 (M^+), 297, 281, 253, 226.

PREPARATION 83

5

Ethyl (Z)-3-(4-ethoxy-3-methoxyphenyl)cinnamate

10 Prepared as an oil, in a yield of 21%.

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

1.15 (3H, triplet, $J = 7.32$ Hz);

1.49 (3H, triplet, $J = 7.32$ Hz);

3.80 (3H, singlet);

15 4.08 (2H, quartet, $J = 7.32$ Hz);

4.14 (2H, quartet, $J = 7.32$ Hz);

6.28 (1H, singlet);

6.73 (1H, doublet, $J = 1.95$ Hz);

6.79 (1H, doublet of doublets, $J = 8.30$ & 1.95 Hz);

20 6.87 (1H, doublet, $J = 8.30$ Hz);

7.29 - 7.40 (5H, multiplet).

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

1710, 1605, 1580, 1515, 1480, 1470, 1450, 1410, 1370, 1355, 1320, 1250, 1160, 1130.

Mass Spectrum (m/z):

25 326 (M^+), 297, 281, 253, 226.

PREPARATION 84

30

(E)-3-(4-Ethoxy-3-methoxyphenyl)cinnamic acid

Prepared as crystals, melting at $200 - 202^\circ C$ (after recrystallization from a mixture of tetrahydrofuran and hexane), in a yield of 93%.

35 Nuclear Magnetic Resonance Spectrum (a 1 : 1 by volume mixture of $CDCl_3$ and CD_3OD , 270 MHz) δ ppm:

1.45 (3H, triplet, $J = 6.96$ Hz);

3.80 (3H, singlet);

40 4.11 (2H, quartet, $J = 6.96$ Hz);

6.32 (1H, singlet);

6.80 (1H, doublet of doublets, $J = 8.43$ & 1.83 Hz);

6.84 (1H, doublet, $J = 8.43$ Hz);

6.88 (1H, doublet, $J = 1.83$ Hz);

45 7.18 - 7.27 (2H, multiplet);

7.32 - 7.42 (3H, multiplet).

Infrared Absorption Spectrum (KBr) ν_{max} cm^{-1} :

2400 - 3600 (broad), 1692, 1660, 1605, 1587, 1514, 1479, 1421, 1402, 1324, 1297, 1274, 1255, 1204, 1137.

Mass Spectrum (m/z):

50 298 (M^+), 270, 253, 225.

PREPARATION 85

55

(Z)-3-(4-Ethoxy-3-methoxyphenyl)cinnamic acid

EP 0 395 446 A2

Prepared as crystals, melting at 133 - 135 °C (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 90%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1.49 (3H, triplet, J = 7.33 Hz);

3.80 (3H, singlet);

4.14 (2H, quartet, J = 7.32 Hz);

6.25 (1H, singlet);

6.72 - 6.86 (3H, multiplet);

7.27 - 7.43 (5H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1690, 1605, 1580, 1515, 1470, 1450, 1415, 1255, 1135.

Mass Spectrum (m/z):

298 (M⁺), 270, 253, 225.

15

PREPARATION 86

20 Ethyl (E)-3-(4-butoxy-3-methoxyphenyl)cinnamate

Prepared as an oil, in a yield of 21%. Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1.43 - 1.54 (2H, multiplet);

1.78 - 1.86 (2H, multiplet);

3.80 (3H, singlet);

4.02 (2H, triplet, J = 6.84 Hz);

4.03 (2H, quartet, J = 7.33 Hz);

6.31 (1H, singlet);

6.77 (2H, broad singlet);

6.79 (2H, broad singlet);

7.17 - 7.24 (2H, multiplet);

7.34 - 7.41 (3H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1710, 1690, 1610, 1595, 1580, 1510, 1465, 1370, 1290, 1270, 1250, 1160, 1135.

Mass Spectrum (m/z):

354 (M⁺), 309, 298, 269, 253, 226.

40

PREPARATION 87

Ethyl (Z)-3-(4-butoxy-3-methoxyphenyl)cinnamate

45

Prepared as an oil, in a yield of 47%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

0.98 (3H, triplet, J = 7 Hz);

1.13 (3H, triplet, J = 7 Hz);

1.30 - 2.20 (4H, multiplet);

3.78 (3H, singlet);

4.02 (2H, triplet, J = 7 Hz);

4.10 (2H, quartet, J = 7 Hz);

6.30 (1H, singlet);

6.70 - 7.05 (3H, multiplet).

PREPARATION 885 (E)-3-(4-Butoxy-3-methoxyphenyl)cinnamate

Prepared as crystals, melting at 140 - 143° C (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 92%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 10 0.97 (3H, triplet, J = 7.33 Hz);
 1.40 - 1.60 (2H, multiplet);
 1.75 - 1.90 (2H, multiplet);
 3.79 (3H, singlet);
 4.02 (2H, triplet, J = 6.84 Hz);
 15 6.28 (1H, singlet);
 6.75 (1H, doublet of doublets, J = 8.78 & 1.47 Hz);
 6.78 (1H, doublet, J = 8.78 Hz);
 6.85 (1H, doublet, J = 1.47 Hz);
 7.17 - 7.24 (2H, multiplet);
 20 7.30 - 7.40 (3H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

2400 - 3600 (broad), 1690, 1610, 1595, 1580, 1510, 1500, 1470, 1420, 1320, 1250, 1135.

Mass Spectrum (m/z):

326 (M⁺), 270, 253, 237.

25

PREPARATION 89

30

Ethyl (Z)-3-(3,4-dichlorophenyl)-3-(4-ethylphenyl)acrylate

Prepared as an oil, in a yield of 50%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 35 1.16 (3H, triplet, J = 7.32 Hz);
 1.24 (3H, triplet, J = 7.32 Hz);
 2.66 (2H, quartet, J = 7.32 Hz);
 4.08 (2H, quartet, J = 7.32 Hz);
 6.37 (1H, singlet);
 40 7.06 (1H, doublet of doublets, J = 8.30 & 1.95 Hz);
 7.12 - 7.24 (4H, multiplet);
 7.30 (1H, doublet, J = 1.95 Hz);
 7.46 (1H, doublet, J = 8.30 Hz).

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

- 45 1710, 1620, 1610, 1470, 1370, 1275, 1170, 1160.

Mass Spectrum (m/z):

348 (M⁺, ³⁵Cl), 319, 303, 276.

50

PREPARATION 90Ethyl (E)-3-(3,4-dichlorophenyl)-3-(4-ethylphenyl)acrylate

55

Prepared as an oil, in a yield of 14%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

1.10 (3H, triplet, J = 7 Hz);

EP 0 395 446 A2

- 1.27 (3H, triplet, $J = 7$ Hz);
2.70 (2H, quartet, $J = 7$ Hz);
4.05 (2H, quartet, $J = 7$ Hz);
6.27 (1H, singlet);
5 6.98 - 7.60 (7H, multiplet).

PREPARATION 91

10

(Z)-3-(3,4-Dichlorophenyl)-3-(4-ethylphenyl)acrylic acid

- Prepared as crystals, melting at $172 - 174^{\circ}\text{C}$ (after recrystallization from a mixture of methylene
15 chloride and hexane), in a yield of 94%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.24 (3H, triplet, $J = 7.32$ Hz);
2.66 (2H, quartet, $J = 7.32$ Hz);
6.35 (1H, singlet);
20 7.06 (1H, doublet of doublets, $J = 7.82$ & 1.95 Hz);
7.12 - 7.24 (4H, multiplet);
7.29 (1H, doublet, $J = 1.95$ Hz);
7.45 (1H, doublet, $J = 7.82$ Hz).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
25 2400 - 3600 (broad), 1690, 1620, 1605, 1470, 1280, 1180, 1160, 1120.
Mass Spectrum (m/z):
320 (M^+ , ^{35}Cl), 305, 291, 275.

30

PREPARATION 92

Ethyl (Z)-3-(4-propoxyphenyl)cinnamate

35

Prepared as an oil, in a yield of 35%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.05 (3H, triplet, $J = 7.33$ Hz);
1.67 (3H, triplet, $J = 7.33$ Hz);
40 1.75 - 1.90 (2H, multiplet);
3.95 (2H, triplet, $J = 6.60$ Hz);
4.09 (2H, quartet, $J = 7.33$ Hz);
6.26 (1H, singlet);
6.89 (2H, doublet of multiplets, $J = 8.80$ Hz);
45 7.14 (2H, doublet of multiplets, $J = 8.80$ Hz);
7.26 - 7.40 (5H, multiplet).
Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1710, 1610, 1510, 1370, 1290, 1260, 1240, 1170.
Mass Spectrum (m/z):
50 310 (M^+), 268, 265, 238, 223, 196.

55

PREPARATION 93

Ethyl (E)-3-(4-propoxyphenyl)cinnamate

EP 0 395 446 A2

Prepared as an oil, in a yield of 35%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.03 (3H, triplet, $J = 7.33$ Hz);
 - 1.10 (3H, triplet, $J = 7.33$ Hz);
 - 5 1.75 - 1.90 (2H, multiplet);
 - 3.92 (2H, triplet, $J = 6.84$ Hz);
 - 4.03 (2H, quartet, $J = 7.33$ Hz);
 - 6.30 (1H, singlet);
 - 6.82 (2H, doublet of multiplets, $J = 9.27$ Hz);
 - 10 7.15 - 7.28 (2H, multiplet);
 - 7.23 (2H, doublet of multiplets, $J = 9.27$ Hz);
 - 7.28 - 7.43 (3H, multiplet).
- Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
1710, 1605, 1595, 1575, 1510, 1370, 1250, 1160, 1150. Mass Spectrum (m/z):
15 310 (M^+), 268, 265, 238, 223, 196.

PREPARATION 94

20

(Z)-3-(4-Propoxyphenyl)cinnamic acid

- Prepared as crystals, melting at $183 - 185^\circ\text{C}$ (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 93%.

25 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.06 (3H, triplet, $J = 7.33$ Hz);
 - 1.75 - 1.90 (2H, multiplet);
 - 3.95 (2H, triplet, $J = 6.84$ Hz);
 - 30 6.23 (1H, singlet);
 - 6.88 (2H, doublet of multiplets, $J = 8.79$ Hz);
 - 7.15 (2H, doublet of multiplets, $J = 8.79$ Hz);
 - 7.26 - 7.42 (5H, multiplet).
- Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :
35 2400 - 3600 (broad), 1695, 1610, 1515, 1290, 1280, 1250, 1175.
- Mass Spectrum (m/z):
282 (M^+), 240, 223, 195.

40

PREPARATION 95

(E)-3-(4-Propoxyphenyl)cinnamic acid

45

Prepared as crystals, melting at $138 - 140^\circ\text{C}$ (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 92%.

Nuclear Magnetic Resonance Spectrum (CDCl_3 , 60 MHz) δ ppm:

- 1.00 (2H, triplet, $J = 7$ Hz);
- 50 1.45 - 2.20 (2H, multiplet);
- 3.90 (2H, quartet, $J = 7$ Hz);
- 6.27 (1H, singlet);
- 6.83 (2H, doublet of multiplets, $J = 9$ Hz);
- 7.05 - 7.60 (7H, multiplet);
- 55 10.00 (1H, broad multiplet).

PREPARATION 965 (E)-3-(3,4-Methylenedioxyphenyl)cinnamic acid

Prepared as crystals, melting at 222 - 224 °C (after recrystallization from a mixture of diethyl ether and tetrahydrofuran), in a yield of 22%.

Nuclear Magnetic Resonance Spectrum (a 1 : 1 by volume mixture of CDCl_3 and CD_3OD , 60 MHz) δ ppm:

- 10 5.99 (2H, singlet);
 6.29 (1H, singlet);
 6.79 (3H, singlet);
 7.05 - 7.60 (5H, multiplet).

15

PREPARATION 97

20

(Z)-3-(3,4-Methylenedioxyphenyl)cinnamic acid

Prepared as crystals, melting at 141 - 143 °C (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 51%.

25 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 60 MHz) δ ppm:

- 6.00 (2H, singlet);
 6.26 (1H, singlet);
 6.72 - 6.96 (3H, multiplet);
 7.15 - 7.55 (5H, multiplet).

30

PREPARATION 98

35

Ethyl (E)-3-(3-methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acrylate

Prepared as an oil, in a yield of 22%.

40 Nuclear Magnetic Resonance Spectrum (CDCl_3 , 270 MHz) δ ppm:

- 1.03 (3H, triplet, $J = 7.32$ Hz);
 1.11 (3H, triplet, $J = 7.32$ Hz);
 1.80 - 1.95 (2H, multiplet);
 2.35 (3H, singlet);
 45 3.81 (3H, singlet);
 3.98 (2H, triplet, $J = 6.84$ Hz);
 4.04 (2H, quartet, $J = 7.32$ Hz);
 6.29 (1H, singlet);
 6.72 - 6.86 (2H, multiplet);
 50 6.90 (1H, broad singlet);
 6.98 - 7.05 (2H, multiplet);
 7.15 - 7.24 (1H, multiplet);
 7.30 - 7.42 (1H, multiplet).

Infrared Absorption Spectrum (CHCl_3) ν_{max} cm^{-1} :

55 1710, 1600, 1580, 1510, 1485, 1370, 1290, 1260, 1160, 1145, 1130.

Mass Spectrum (m/z):

354 (M^+), 312, 267, 240.

PREPARATION 995 Ethyl (Z)-3-(3-methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acrylate

Prepared as an oil, in a yield of 40%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.05 (3H, triplet, J = 7.32 Hz);
 10 1.15 (3H, triplet, J = 7.32 Hz);
 1.80 - 1.95 (2H, multiplet);
 2.32 (3H, singlet);
 3.80 (3H, singlet);
 4.02 (2H, triplet, J = 6.84 Hz);
 15 4.08 (2H, quartet, J = 7.32 Hz);
 6.26 (1H, singlet);
 6.72 (1H, doublet, J = 1.96 Hz);
 6.78 (1H, doublet of doublets, J = 7.82 & 1.96 Hz);
 6.87 (1H, doublet, J = 7.82 Hz);
 20 7.06 - 7.25 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

1710, 1605, 1590, 1515, 1465, 1370, 1250, 1180, 1160, 1130.

Mass Spectrum (m/z):

354 (M⁺), 312, 267, 240.

25

PREPARATION 100

30

(E)-3-(3-methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acrylic acid

Prepared as crystals, melting at 123 - 126° C (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 98%.

35 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

- 1.03 (3H, triplet, J = 7.33 Hz);
 1.75 - 1.95 (2H, multiplet);
 2.34 (3H, singlet);
 3.80 (3H, singlet);
 40 3.98 (2H, triplet, J = 6.84 Hz);
 6.26 (1H, singlet);
 6.74 (1H, doublet of doublets, J = 8.79 & 1.93 Hz);
 6.78 (1H, doublet, J = 8.79 Hz);
 6.86 (1H, doublet, J = 1.95 Hz);
 45 6.98 - 7.05 (2H, multiplet);
 7.14 - 7.30 (2H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1690, 1595, 1580, 1515, 1470, 1260, 1175, 1145, 1130.

Mass Spectrum (m/z):

50 326 (M⁺), 284, 267, 239.

55

PREPARATION 101(Z)-3-(3-methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acrylic acid

Prepared as crystals, melting at 132 - 135 °C (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 97%.

5

PREPARATION 102Ethyl 3,3-bis(3-methylphenyl)acrylate

10

Prepared as an oil, in a yield of 78%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

1.11 (3H, triplet, J = 7.32 Hz);

2.32 (3H, singlet);

15 2.35 (3H, singlet);

4.03 (2H, quartet, J = 7.32 Hz);

6.31 (1H, singlet);

6.98 - 7.30 (8H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

20 1710, 1620, 1600, 1580, 1370, 1350, 1280, 1190, 1160.

Mass Spectrum (m/z):

280 (M⁺), 265, 251, 235, 208.

25

PREPARATION 1033,3-Bis(3-methylphenyl)acrylic acid

30

Prepared as crystals, melting at 133 - 135 °C (after recrystallization from a mixture of methylene chloride and hexane), in a yield of 94%.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.32 (3H, singlet);

35 2.34 (3H, singlet);

6.28 (1H, singlet);

6.98 - 7.12 (4H, multiplet);

7.14 - 7.30 (4H, multiplet).

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

40 2400 - 3600 (broad), 1690, 1615, 1600, 1580, 1430, 1285, 1170.

Mass Spectrum (m/z):

252 (M⁺), 237, 235, 207.

45

PREPARATION 104Methyl (E)-3,5-diphenylpent-2-en-4-ynoate

50

0.158 g of cuprous iodide and 0.424 g of phenylacetylene were added to 25 ml of a diethylamine solution containing 1.000 g of methyl (Z)-3-bromocinnamate and 0.029 g of bis(triphenylphosphine)-dichloropalladium. The mixture was then stirred for 1 hour at room temperature, after which the solvent was distilled off under reduced pressure. Water was added to the residue, and the resulting mixture was extracted twice with benzene. The combined benzene extracts were washed with water, dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure. The residue was subjected to column chromatography through silica gel (70 - 230 Tyler mesh, 25 g). Those fractions eluted with a 39 : 1 by volume mixture of hexane and ethyl acetate were collected to afford 1.043 g of the title

EP 0 395 446 A2

compound, melting at 73° - 75° C (after recrystallisation from hexane).

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

3.84 (3H, singlet);

6.60 (1H, singlet);

5 7.34 - 7.82 (10H, multiplet).

Mass spectrum (m/z):

262 (M⁺); 247, 231.

Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

2200, 1710, 1600, 1590, 1575, 1490, 1450, 1435, 1365, 1275, 1165.

10

PREPARATION 105

15

(E)-3,5-Diphenylpent-2-en-4-ynoic acid

A mixture of 1.000 g of methyl (E)-3,5-diphenylpent-2-en-4-ynoate (prepared as described in Preparation 104), 15 ml of methanol, 7.5 ml of tetrahydrofuran and 15 ml of a 10% w/v aqueous solution of sodium hydroxide was stirred for 18 hours at room temperature. At the end of this time, the solvent was distilled off under reduced pressure. The resulting residue was diluted with water and extracted twice with diethyl ether. The ethereal extracts were washed with water, dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure, to give 0.912 g of the title compound, melting at 124° - 126° C (after recrystallisation from a mixture of methylene chloride and hexane).

25 Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

6.65 (1H, singlet);

7.30 - 7.90 (10H, multiplet).

Mass spectrum (m/z):

248 (M⁺), 231, 220.

30 Infrared Absorption Spectrum (CHCl₃) ν_{max} cm⁻¹:

2400 - 3600 (broad), 2200, 1685, 1600, 1590, 1575, 1490, 1450, 1280, 1180.

PREPARATION 106

35

Ethyl 3,3-bis(4-methoxyphenyl)-3-hydroxy-2-methylpropionate

40 A mixture of 8.25 g of ethyl 2-bromopropionate, 11.81 g of 4,4'-dimethoxybenzophenone, 7.16 g of zinc and 70 ml of benzene was heated on an oil bath for 4 hours under reflux. The mixture was then allowed to stand to cool, after which the reaction solution was filtered. The filtrate was washed with 10% w/v aqueous sulphuric acid, with water and with a saturated aqueous solution of sodium chloride, in that order. After the mixture had been dried, the solvent was distilled off under reduced pressure. The residue was subjected to

45 flash column chromatography through silica gel (about 400 mesh, 300 g). 7.92 g of the title compound were obtained as white crystals, melting at 67° - 69° C (after recrystallisation from a mixture of methylene chloride and hexane), from those fractions eluted with a 100 : 2 by volume mixture of hexane and ethyl acetate.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

50 1.14 (6H, triplet, J = 6.84 Hz);

3.54 (1H, quartet, J = 6.84 Hz);

3.75 (6H, singlet);

3.95 - 4.15 (2H, multiplet);

4.61 (1H, singlet);

55 6.80 (4H, doublet of multiplets, J = 8.79 Hz);

7.33 (2H, doublet of multiplets, J = 8.79 Hz);

7.44 (2H, doublet of multiplets, J = 8.79 Hz).

Mass spectrum (m/z):

344 (M^+), 326, 299, 281, 243.

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

1710, 1610, 1510, 1460, 1375, 1340, 1245, 1170.

5

Elemental analysis:	
Calculated for $C_{20}H_{24}O_5$:	
Found:	C, 69.75%; H, 7.02%.
	C, 69.89%; H, 7.10%.

10

15

PREPARATION 107

Ethyl 3,3-bis(4-methoxyphenyl)-2-methylacrylate

20

4.10 ml of phosphorus oxychloride were dropped at from 5° to 10° C onto 140 ml of a benzene solution containing 7.02 g of ethyl 3,3-bis(4-methoxyphenyl)-3- hydroxy-2-methylpropionate (prepared as described in Preparation 106) on an ice bath. The reaction solution was then stirred for 3 hours at room temperature, after which it was poured into water and then extracted with diethyl ether three times. The combined

25 ethereal extracts were washed with a saturated aqueous solution of sodium bicarbonate, with water and with a saturated aqueous solution of sodium chloride, after which it was dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure. The residue (6.72 g) was subjected to flash column chromatography through 100 g of silica gel. 6.04 g of the title compound were obtained as an oily substance from those fractions eluted with a 95 : 5 by volume mixture of hexane and ethyl acetate.

30

Nuclear Magnetic Resonance Spectrum ($CDCl_3$, 270 MHz) δ ppm:

0.95 (3H, triplet, $J = 7.32$ Hz);

2.05 (3H, singlet);

3.78 (3H, singlet);

3.81 (2H, singlet);

35

3.97 (2H, quartet, $J = 7.32$ Hz);

6.79 (2H, doublet of multiplets, $J = 8.30$ Hz);

6.85 (2H, doublet of multiplets, $J = 8.30$ Hz);

7.03 (2H, doublet of multiplets, $J = 8.30$ Hz);

7.08 (2H, doublet of multiplets, $J = 8.30$ Hz).

40

Mass spectrum (m/z):

326 (M^+), 297, 281, 271, 252.

Infrared Absorption Spectrum ($CHCl_3$) ν_{max} cm^{-1} :

1700, 1610, 1510, 1465, 1315, 1300, 1280, 1240, 1175, 1125.

45

Elemental analysis:	
Calculated for $C_{20}H_{22}O_4$:	
Found:	C, 73.60%; H, 6.79%.
	C, 73.39%; H, 6.82%.

50

55

PREPARATION 108

3,3-Bis(4-methoxyphenyl)-2-methylacrylic acid

A mixture of 6.019 g of ethyl 3,3-bis(4-methoxyphenyl)acrylate (prepared as described in Preparation 107), 120 ml of ethanol and 80 ml of a 10% w/v aqueous solution of sodium hydroxide was stirred for 14 hours at room temperature. At the end of this time, the reaction mixture was heated on an oil bath at 100 °C for 4 hours, and then ethanol was distilled off. The residue was diluted with ice-water and washed with ethyl acetate. Concentrated hydrochloric acid was dropped onto the aqueous phase on an ice bath, to adjust the pH to a value of 2. The aqueous phase was extracted twice with methylene chloride. The combined methylene chloride extracts were washed with water, dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure, to afford 5.117 g of the title compound as white crystals, melting at 134 ° - 135 ° C (after recrystallisation from a mixture of methylene chloride and hexane).

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

2.06 (3H, singlet);

3.80 (3H, singlet);

15 3.81 (3H, singlet);

6.79 (2H, doublet of multiplets, J = 8.79 Hz);

6.86 (2H, doublet of multiplets, J = 8.79 Hz);

7.06 (2H, doublet of multiplets, J = 8.79 Hz);

7.07 (2H, doublet of multiplets, J = 8.79 Hz).

20 Mass spectrum (m/z):

298 (M⁺), 281, 253.

Infrared Absorption Spectrum (CHCl₃) ν_{\max} cm⁻¹:

2400 - 3600 (broad), 1680, 1610, 1510, 1245, 1175.

25

Elemental analysis:	
Calculated for C ₁₈ H ₁₈ O ₄ :	
Found:	C, 72.47%; H, 6.08%.
	C, 72.11%; H, 6.15%.

30

35

PREPARATION 109N-(3,4,5-Trimethoxybenzenesulphonyl)piperazine

40

75 ml of a methylene chloride solution containing 7.40 g of 3,4,5-trimethoxybenzenesulphonyl chloride were dropped into 150 ml of a methylene chloride solution containing 3.80 g of N-formylpiperazine and 7.73 ml of triethylamine in an ice bath. The mixture was then stirred for 30 minutes at 0 ° to 5 ° C, after which it was poured into water and extracted twice with methylene chloride. The combined methylene chloride extracts were washed with 10% w/v aqueous hydrochloric acid and with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure. The residue (9.86 g) was dissolved in a mixture of 150 ml of tetrahydrofuran, 75 ml of methanol and 50 ml of a 10% w/v aqueous solution of sodium hydroxide, and then stirred for 14 hours at room temperature. At the end of this time, the reaction solution was poured into water and extracted 4 times with methylene chloride. The combined methylene chloride extracts were washed with water, dried over anhydrous sodium sulphate and condensed by evaporation under reduced pressure. The residue was crystallized from a mixture of hexane and ethyl acetate, to give 7.02 g of the title compound as crystals, melting at 131 to 133 ° C.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 270 MHz) δ ppm:

55 2.90 - 3.10 (8H, multiplet);

3.91 (9H, singlet);

6.96 (2H, singlet).

Mass spectrum (m/z):

316 (M⁺), 232, 85.

5

Elemental analysis:	
Calculated for C ₁₃ H ₂₀ N ₂ O ₅ S:	
Found:	C, 49.35%; H, 6.37%; N, 8.85%; S, 10.13%. C, 49.62%; H, 6.30%; N, 8.55%; S, 10.11%.

10

PREPARATION 110

15

3,3-Bis(3-chlorophenyl)acrylic acid

Following a procedure similar to that described in Preparation 1, but using 10.85 g of 3,3'-dichlorobenzophenone, 12.32 g of the title compound, melting at 114 - 115°C, were obtained after recrystallization from a mixture of methylene chloride and hexane.

25

PREPARATION 111

1-[3,3-Bis(3-chlorophenyl)acryloyl]piperazine

5.51 ml of diphenylphosphoryl azide and 1.93 ml of N-formylpiperazine were added, in that order, to 100 ml of a methylene chloride solution containing 5.00 g of 3,3-bis(3-chlorophenyl)acrylic acid (prepared as described in Preparation 110) and 4.75 ml of triethylamine. The reaction mixture was then stirred at room temperature for 18 hours, after which it was washed with a saturated aqueous solution of sodium bicarbonate and then with water. It was then dried over anhydrous sodium sulphate and the solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixture of 100 ml of ethanol and 50 ml of tetrahydrofuran, and 50 ml of a 10% w/v aqueous solution of sodium hydroxide were added. The resulting mixture was stirred for 8 hours at room temperature, after which it was poured into water. The solution was extracted twice, each time with methylene chloride, and the combined extracts were washed with water and dried over anhydrous sodium sulphate; the solvent was then removed by distillation under reduced pressure. The resulting residue was purified by column chromatography through 150 g of silica gel, using mixtures of methylene chloride and methanol ranging from 49 : 1 to 9 : 1 by volume as eluent, to give 5.23 g of the title compound as a viscous oil.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

2.21 (1H, singlet);

45 2.00 - 2.95 (4H, multiplet);

3.00 - 3.85 (4H, multiplet);

6.38 (1H, singlet);

6.90 - 7.50 (8H, multiplet).

Mass Spectrum (m/z):

50 360 (M⁺, ³⁵Cl), 325, 292, 275.

PREPARATION 112

55

Ethyl (Z) and (E)-3-(2-naphthyl)-3-phenylacrylate

A procedure similar to that described in the first half of Preparation 1 was repeated, except that 10.10 g of β -naphthyl phenyl ketone were used. The resulting crude compound was purified by column chromatography through 200 g of silica gel and then by medium pressure liquid chromatography through a Lobar C column, eluted with mixtures of hexane and ethyl acetate, to give 2.48 g of the Z-isomer of the title compound, melting at 91 - 92° C, after recrystallization from hexane.

Further elution with the same solvent gave 4.44 g of the E-isomer, melting at 84 - 85° C, after recrystallization from hexane.

PREPARATION 113

(Z)-3-(2-Naphthyl)-3-phenylacrylic acid

24 ml of a 10% w/v aqueous solution of sodium hydroxide were added to a solution of 2.411 g of ethyl (Z)-3-(2-naphthyl)-3-phenylacrylate (prepared as described in Preparation 112) in 48 ml of ethanol and 24 ml of tetrahydrofuran. The mixture was stirred for 15 hours at room temperature and then poured into water. The pH of the resulting mixture was adjusted to a value of 2 by the addition of concentrated hydrochloric acid, and the mixture was then extracted twice with methylene chloride. The combined extracts were washed with water and dried over anhydrous sodium sulphate; the solvent was then removed by evaporation under reduced pressure. The residue was recrystallized from a mixture of methylene chloride and hexane, to give 2.005 g of the title compound, melting at 170 - 172° C.

Nuclear Magnetic Resonance Spectrum (a 1 : 1 by volume mixture of CDCl_3 and CD_3OD , 60 MHz) δ ppm:

6.44 (1H, singlet);
7.28 - 7.42 (6H, multiplet);
7.44 - 7.54 (2H, multiplet);
7.71 (1H, doublet, $J = 0.73$ Hz);
7.76 - 7.91 (3H, multiplet).
Mass Spectrum (m/z):
274 (M^+), 257, 229.

Elemental analysis:	
Calculated for $\text{C}_{19}\text{H}_{14}\text{O}_2$:	
Found:	C, 83.19%; H, 5.14%.
	C, 83.39%; H, 5.35%.

PREPARATION 114

(E)-3-(2-Naphthyl)-3-phenylacrylic acid

A hydrolysis procedure similar to that described in Preparation 113 was repeated, except that 2.219 g of ethyl (E)-3-(2-naphthyl)-3-phenylacrylate (prepared as described in Preparation 112) were used, to give 1.685 g of the title compound, melting at 229 - 231° C, after recrystallization from a mixture of diethyl ether and tetrahydrofuran.

Nuclear Magnetic Resonance Spectrum (a 1 : 1 by volume mixture of CDCl_3 and CD_3OD , 60 MHz) δ ppm:

6.50 (1H, singlet);
7.23 - 7.32 (2H, multiplet);
7.36 - 7.43 (3H, multiplet);
7.43 - 7.54 (3H, multiplet);
7.67 (1H, doublet, $J = 1.83$ Hz);

7.70 - 7.88 (3H, multiplet).

Mass Spectrum (m/z):

274 (M^+), 257, 229.

Elemental analysis:

Calculated for $C_{19}H_{14}O_2$:

C, 83.19%; H, 5.14%.

Found: C, 83.45%; H, 5.33%.

PREPARATION 115

Ethyl (E)-p-isobutoxycinnamate

13.8 g of potassium carbonate and 7.50 g of sodium iodide were added to a solution of 9.61 g of ethyl (E)-p-hydroxycinnamate and 8.22 g of isobutylbromide in 100 ml of dimethyl sulphoxide. The reaction mixture was then stirred for 20 hours at 60 °C, after which it was cooled to the room temperature. The reaction mixture was then poured into 1 liter of water and extracted twice with ethyl acetate. The combined

extracts were washed with water and dried over anhydrous sodium sulphate; the solvent was then removed by evaporation under reduced pressure. The residue was purified by flash column chromatography using 300 g of silica gel, eluted with a 5 : 1 by volume solution of hexane and ethyl acetate, to give 10.71 g of the title compound as a colourless oil (which solidified at low temperature).

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

0.98 (6H, doublet, J = 7 Hz);
1.28 (3H, triplet, J = 7 Hz);
1.60 - 2.50 (1H, multiplet);
3.70 (2H, doublet, J = 7 Hz);
4.24 (2H, quartet, J = 7 Hz);
6.26 (1H, doublet, J = 16 Hz);
6.86 (2H, doublet of multiplets, J = 9 Hz);
7.45 (2H, doublet of multiplets, J = 9 Hz);
7.66 (1H, doublet, J = 16 Hz).

PREPARATION 116

Ethyl (E)-p-propoxycinnamate

Following a procedure similar to that described in Preparation 115, but using 9.61 g of ethyl (E)-p-hydroxycinnamate and 10.20 g of propyl iodide and not using sodium iodide, 11.00 g of the title compound were obtained as a solid material.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

0.98 (3H, triplet, J = 7 Hz);
1.26 (3H, triplet, J = 7 Hz);
1.20-2.20 (2H, multiplet);
3.88 (2H, triplet, J = 6.5 Hz);
4.21 (2H, quartet, J = 7 Hz);
6.24 (1H, doublet, J = 16 Hz);
6.85 (2H, doublet of multiplets, J = 8 Hz);
7.44 (2H, doublet of multiplets, J = 8 Hz);

7.62 (1H, doublet, J = 16 Hz).

PREPARATION 117

5

Ethyl (E)-3,4-dipropoxycinnamate

10 Following a procedure similar to that described in Preparation 116, but using 10.41 g of ethyl (E)-3,4-dihydroxycinnamate and 20.40 g of propyl iodide, 10.20 g of the title compound were obtained as a solid material.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

1.02 (6H, triplet, J = 7 Hz);
15 1.32 (3H, triplet, J = 7 Hz);
1.50-2.20 (4H, multiplet);
3.99 (4H, triplet, J = 7 Hz);
4.26 (2H, quartet, J = 7 Hz);
6.30 (1H, doublet, J = 16 Hz);
20 6.70 - 7.35 (3H, multiplet);
7.65 (1H, doublet, J = 16 Hz).

PREPARATION 118

25

Ethyl (E)-4-ethoxy-3-methoxycinnamate

30 Following a procedure similar to that described in Preparation 116, but using 5.83 g of ethyl (E)-4-hydroxy-3-methoxycinnamate and 5.61 g of ethyl iodide, 5.55 g of the title compound were obtained as a solid material.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

1.30 (3H, triplet, J = 7 Hz);
35 1.44 (3H, triplet, J = 7 Hz);
3.89 (3H, singlet);
4.14 (2H, quartet, J = 7 Hz);
4.24 (2H, quartet, J = 7 Hz);
6.30 (1H, doublet, J = 16 Hz);
40 6.75 - 7.35 (3H, multiplet);
7.66 (1H, doublet, J = 7 Hz).

PREPARATION 119

45

Ethyl (E)-3-methoxy-4-propoxycinnamate

50 Following a procedure similar to that described in Preparation 116, but using 11.11 g of ethyl (E)-4-hydroxy-3-methoxycinnamate and 10.20 g of propyl iodide, 12.08 g of the title compound were obtained.

Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

1.01 (3H, triplet, J = 7 Hz);
1.30 (3H, triplet, J = 7 Hz);
55 1.50 - 2.20 (2H, multiplet);
3.88 (3H, singlet);
3.98 (2H, triplet, J = 7 Hz);
4.24 (2H, quartet, J = 7 Hz);

6.28 (1H, doublet, J = 16 Hz);
 6.70 - 7.35 (3H, multiplet);
 7.65 (1H, doublet, J = 16 Hz).

5

PREPARATION 12010 Ethyl (E)-4-butoxy-3-methoxycinnamate

Following a procedure similar to that described in Preparation 116, but using 6.66 g of ethyl (E)-4-hydroxy-3-methoxycinnamate and 6.62 g of butyl iodide, 7.00 g of the title compound were obtained as a solid material.

15 Nuclear Magnetic Resonance Spectrum (CDCl₃, 60 MHz) δ ppm:

0.96 (3H, triplet, J = 7 Hz);
 1.30 (3H, triplet, J = 7 Hz);
 1.20 - 2.10 (4H, multiplet);
 3.88 (3H, singlet);
 4.03 (3H, triplet, J = 7 Hz);
 4.24 (2H, quartet, J = 7 Hz);
 6.28 (1H, doublet, J = 16 Hz);
 6.75 - 7.35 (3H, multiplet);
 7.65 (1H, doublet, J = 16 Hz).

25

EXPERIMENT 1

30

Inhibition of PAF-induced hypotension

The test animals used were Wistar-Imamichi rats, each weighing from 350 to 450 g, anesthetized with Inactin (90 mg/kg, intraperitoneally).

35

Blood pressure was continuously measured throughout the experiment through a cannula inserted into the femoral artery. Each drug sample to be tested was intravenously injected through a cannula inserted into the femoral vein.

40

At first, β -C_{16:0} PAF was injected intravenously in amounts of 10 ng/kg at each injection at intervals of 5 minutes until the degree of the hypotensive response became constant. Then, each drug sample to be tested was intravenously injected. After one minute, the same dose of PAF was administered again. The drug sample was cumulatively administered. From its inhibition rate against the PAF-induced hypotensive effect, the 50% inhibitive dose (ID₅₀) was determined, and is regarded as an index of PAF-antagonist activity. For administration, the PAF was dissolved in physiological saline solution containing 0.25% w/v of bovine serum albumin (BSA). The compounds under test were dissolved in dimethylformamide for use.

45

In addition to the compounds of the invention that were tested, we also tested a prior art compound, CV-3988, under the same conditions, so as to show the extent of the improvement in activity achieved by the compounds of the invention as compared with what is recognised to be one of the most effective of the available prior art compounds. CV-3988 is disclosed in US Patent No. 4 408 052, and is structurally related to PAF itself.

50

Table 4 below shows the results. In this Table, the compounds of the invention are identified by the number of the foregoing Example in which they were prepared.

55

Table 4

Compound of Example	Inhibitory effect ID ₅₀ (mg/kg)
1	0.057
2	0.039
3	0.048
4	0.074
5	0.054
7	0.014
8	0.058
15	0.022
16	0.074
17	0.0083
18	0.026
25	0.052
28	0.039
29	0.048
30	0.044
31	0.0067
33	0.0078
34	0.021
35	0.012
36	0.039
39	0.0080
41	0.0071
42	0.0050
43	0.0044
44	0.0075
Prior art compound, CV-3988	0.42

EXPERIMENT 2Inhibitory effect in vitro against PAF-induced blood platelet aggregation

Blood samples were drawn from a rabbit and one part by volume of each sample was immediately mixed with 1/9 part of a 3.8% w/v aqueous solution of sodium citrate. The samples were centrifuged at 150 x G at room temperature for 15 minutes to obtain a platelet rich plasma (PRP) fraction from the upper layer. The remains were further centrifuged at 1,000 x G for 15 minutes to obtain a platelet poor plasma (PPP) fraction from the upper layer. The PRP and PPP fractions were mixed appropriately, to obtain a sample in which the final count of blood platelets was adjusted to be 6×10^5 per μl . According to the method reported by Born et al. [G. V. R. Born et al.: J. Physiol. 62, 67-68 (1962)], blood platelet aggregation was determined by an increase in light transmission measured using an aggregometer. 3 μl of a solution of the test compound in dimethyl sulphoxide were added to 272 μl of PRP, and, after 1 minute, 25 μl of a physiological saline solution containing 1-C_{16:0} PAF (at a final concentration of 10^{-8} – 3×10^{-8} M) were added. Inhibition of aggregation was observed for 5 minutes. At the end of this time, the inhibition rate was calculated from this value and the value of PAF-induced aggregation which was observed when dimethyl sulphoxide only was used without the addition of any test compound. IC₅₀ values were calculated from the dose-response curve.

Table 5 below shows the results.

Table 5

Compound of Example	Inhibitory effect IC ₅₀ (M)
1	3.2×10^{-7}
2	2.0×10^{-7}
3	2.2×10^{-7}
5	2.6×10^{-7}
15	6.8×10^{-8}
17	6.3×10^{-8}
28	2.3×10^{-7}
29	1.8×10^{-7}
30	1.5×10^{-7}
31	4.4×10^{-8}
33	4.3×10^{-8}
35	1.1×10^{-7}
36	2.2×10^{-7}
37	1.1×10^{-7}
40	1.1×10^{-7}
41	6.7×10^{-8}
Prior art compound, CV-3988	9.8×10^{-6}

EXPERIMENT 3Inhibitory effect on PAF-receptor binding

Blood samples were drawn from the heart of a rabbit. 1 part by volume of each sample was mixed immediately with 1.9 part of 0.77 M solution of disodium ethylenediaminetetraacetate. After a similar procedure to that described in Experiment 2, a precipitated blood platelet sample was obtained. This blood platelet sample was washed, and, after repeated freezing and thawing for cellular breakdown, it was laid on top of double layers consisting of 0.25 M and 1.5 M sucrose solutions. By centrifugation at 63,500 x G, for 2 hours at 4° C, the fraction obtained from the interface between the 0.25 M and 1.5 M sucrose solutions was collected and is regarded as a PAF-receptor membrane fraction. A receptor binding experiment was conducted according to a method very similar to that reported by Hwang et al. [San-Bao Hwang et al. J. Biol. Chem. 260, 15639-15645 (1985)]. The specific binding of ³H-PAF was measured using a Wattman GF/C filter. A test compound was dissolved in dimethyl sulphoxide and diluted 100 fold with a buffer solution containing 0.5% bovine serum albumin. Nine parts by weight of the solution, for a receptor binding experiment, was mixed with one part of the test compound solution prepared above. The percent inhibition of the specific binding was plotted for a log concentration of the test compound, and the 50% inhibitory concentration (IC₅₀) was calculated from the linear line connecting all the plotted points.

The results are shown in Table 6.

Table 6

Compound of Example	Inhibition of receptor binding (IC_{50} M)
1	4.7×10^{-8}
5	4.7×10^{-8}
15	4.3×10^{-8}
31	1.4×10^{-8}
Prior art compound, CV-3988	1.6×10^{-6}

As can be seen from this table, the novel N-acryloylpiperazine derivatives of the present invention have an excellent PAF-antagonist activity.

EXPERIMENT 4

Acute toxicity

Each of the compounds prepared as described in Examples 2, 7 and 15 was separately administered orally in a dose of 300 mg/kg to each of a group of 3 male ddy mice (5 weeks old). The mice were observed for a period of one week, during which time all mice survived, indicating that the compounds of the present invention have a very low toxicity.

FORMULATION 1

Tablets

The composition was as follows:

Compound of Example 3	50 mg
Lactose	98 mg
Corn starch	30 mg
Microcrystalline cellulose	20 mg
Magnesium stearate	2 mg
	200 mg

All of the above ingredients, except for the magnesium stearate, were blended for 30 minutes, after which the magnesium stearate was added through a screen, and the mixture was blended for a further 5 minutes. The mixture was then compressed to form tablets of diameter 8 mm.

FORMULATION 2

Capsules

EP 0 395 446 A2

The composition was as follows:

Compound of Example 3	50 mg
Lactose	98 mg
Corn starch	50 mg
Magnesium stearate	2 mg
	200 mg

All of the above ingredients were blended for 5 minutes, after which the mixture was filled into No. 3 capsules.

FORMULATION 3

Granules

The composition was as follows:

Compound of Example 3	50 mg
Lactose	730mg
Corn starch	200 mg
Hydroxypropyl cellulose	20 mg
	1000 mg

The first three of the above ingredients were mixed, and then the mixture was moistened with a 10% aqueous solution of the hydroxypropyl cellulose. The moistened mixture was then granulated by passing it through a basket with an extruder of diameter 0.5 mm. The granules were dried at 60 °C and sized through a 16 mesh screen (Tyler standard mesh).

FORMULATION 4

Suppositories

50 mg of the Compound of Example 3 were dispersed in 1950 mg of Witepsol (trade mark) at 50 °C and poured into an appropriate mold.

FORMULATION 5

Syrups

The composition was as follows:

Compound of Example 3	1 g
Sucros	50 g
Carboxymethylcellulose sodium	0.25 g
Citric acid	0.15 g
Sodium citrate	1 g
Sodium benzoate	0.5 g
Purified Water	100 ml

The sucrose, citric acid, sodium nitrate and sodium benzoate were dissolved in purified water; the carboxymethylcellulose sodium was dispersed in the resulting solution with the active compound, and then the volume was adjusted with more purified water.

FORMULATION 6

Injections

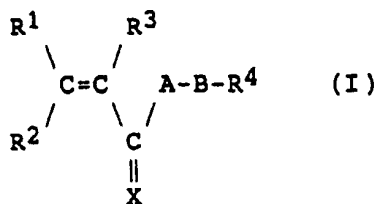
The composition was as follows:

Compound of Example 3	1.0 mg
Propylene glycol	150.0 mg
Polysorbate 80	0.5 mg
Sodium dihydrogen phosphate (dihydrate)	1.6 mg
Disodium hydrogen phosphate (anhydrous)	1.4 mg
Purified water for injection	1.0 ml

The active compound was dissolved in a mixture of the propylene glycol and the Polysorbate 80, and the resulting solution was mixed with water for injection. The phosphates were then dissolved in the solution and the volume was adjusted. The solution was filled into an ampoule, which was then sealed and sterilized at 121 °C for 20 minutes.

Claims

1. Compounds of formula (I):



in which:

R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,

in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a), defined below, or an aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being

- unsubstituted or being substituted by at least one of substituents (a), defined below;
 R³ represents a hydrogen atom, a C₁ - C₆ alkyl group, a cyano group, or a group having the formula -R⁵, in which R⁵ is as defined above;
 X represents an oxygen atom or a sulphur atom;
- 5 A represents a 1,4-piperazin-1,4-diyl group or a 1,4-homopiperazin-1,4-diyl group;
 B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group, a sulphonyl group or a sulphonyl group;
 R⁴ represents an unsubstituted phenyl group or a substituted phenyl group having from 1 to 5 of substituents (a) and/or substituents (b), defined below;
- 10 substituents (a):
 C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; hydroxy groups; C₁ - C₄ alkylenedioxy groups; C₁ - C₂₂ aliphatic carboxylic acyloxy groups; substituted C₁ - C₆ aliphatic carboxylic acyloxy groups which are substituted by at least one of substituents (c), defined below; C₇ - C₁₅ carbocyclic aromatic carboxylic acyloxy groups; substituted C₇ - C₁₅ carbocyclic aromatic carboxylic
 15 acyloxy groups which are substituted by at least one of substituents (d), defined below; C₈ - C₁₅ aralkyloxycarbonyloxy groups in which the aryl part is unsubstituted or is substituted by at least one of substituents (d), defined below; C₁ - C₆ alkanesulphonyloxy groups in which the alkane part is unsubstituted or is substituted by at least one of substituents (c), defined below; arylsulphonyloxy groups in which the aryl part is unsubstituted or is substituted by at least one of substituents (d), defined below; halogen atoms; and
 20 nitro groups;
substituents (b):
 C₁ - C₆ alkylsulphonyl groups; C₁ - C₆ alkylsulphonyl groups; and C₁ - C₆ alkylthio groups;
substituents (c):
 C₁ - C₆ alkyl groups; C₁ - C₆ haloalkyl groups; halogen atoms; C₁ - C₆ alkoxy groups; and (C₁ - C₆
 25 alkanoyloxy)methoxycarbonyl groups;
substituents (d):
 C₁ - C₆ alkyl groups; C₁ - C₆ alkoxy groups; halogen atoms; unsubstituted C₆ - C₁₀ aryl groups; nitro groups; and (C₁ - C₆ alkoxy)carbonyl groups;
 and pharmaceutically acceptable salts thereof.
- 30 2. A compound according to Claim 1, in which:
 R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,
 in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a'), defined below, or an aromatic heterocyclic group having from 5 to 14 ring atoms, of
 35 which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (a'), defined below;
 R⁴ represents an unsubstituted phenyl group or a substituted phenyl group having from 1 to 5 of substituents (a'), defined below, and/or substituents (b), defined in Claim 1;
substituents (a'):
 40 C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; hydroxy groups; C₁ - C₄ alkylenedioxy groups; halogen atoms; and nitro groups.
3. A compound according to Claim 1, in which:
 R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,
 45 in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a''), defined below, or an unsubstituted aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or sulphur hetero-atoms;
 R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;
 A represents a 1,4-piperazin-1,4-diyl group;
 50 B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;
 R⁴ represents a substituted phenyl group having from 1 to 5 of substituents (a''), defined below; and
substituents (a''):
 C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; C₁ - C₄ alkylenedioxy groups; and
 halogen atoms.
- 55 4. A compound according to Claim 3, in which:
 at least one of R¹ and R² represents an aryl group which is substituted by at least one of substituents (a'''), defined in Claim 3;
 R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

X represents an oxygen atom;

A represents a 1,4-piperazin-1,4-diyl group; and

B represents a carbonyl group.

5 5. A compound according to Claim 1, in which R¹ and R² are the same or different and each represents a group of formula -R⁵, in which R⁵ is as defined in Claim 1.

6. A compound according to Claim 1, in which R¹ and R² each represents a group R⁵, and R⁵ represents an aryl group.

7. A compound according to Claim 6, in which one of the groups represented by R⁵ is a substituted phenyl group and the other is an unsubstituted phenyl group or a substituted phenyl group.

10 8. A compound according to Claim 1, in which R¹ represents a substituted phenyl group having at least one of said alkyl, alkoxy or halogen substituents and R² represents an unsubstituted phenyl group or a substituted phenyl group having at least one of said alkyl, haloalkyl and halogen substituents.

9. A compound according to Claim 1, in which R¹ represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl, C₁ - C₂₂ alkoxy or halogen substituent.

15 10. A compound according to Claim 1, in which R¹ represents a substituted phenyl group having at least one C₁ - C₆ alkyl, C₁ - C₆ alkoxy or halogen substituent.

11. A compound according to Claim 1, in which R² represents an unsubstituted phenyl group or a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or C₁ - C₆ haloalkyl and/or halogen substituent.

20 12. A compound according to Claim 1, in which R² represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₆ haloalkyl and/or halogen substituent.

13. A compound according to Claim 1, in which R² represents a substituted phenyl group having at least one C₁ - C₆ alkyl and/or C₁ - C₆ haloalkyl and/or halogen substituent.

25 14. A compound according to any one of Claims 11 to 13, in which the substituent on R² is at the meta position.

15. A compound according to Claim 1, in which R³ represents a hydrogen atom or a C₁ - C₆ alkyl group.

16. A compound according to Claim 1, in which R³ represents a hydrogen atom.

17. A compound according to Claim 1, in which X represents an oxygen atom.

30 18. A compound according to Claim 1, in which B represents a carbonyl group.

19. A compound according to Claim 1, in which R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents.

20. A compound according to Claim 1, in which R⁴ represents a phenyl group having at least one C₁ - C₃ alkoxy substituent.

35 21. A compound according to Claim 1, in which R⁴ represents a 3,4-dimethoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl or 3,4,5-trimethoxyphenyl group.

22. A compound according to Claim 1, in which A represents a 1,4-piperazin-1,4-diyl group.

23. A compound according to Claim 1, in which:

40 R¹ and R² are the same or different and each represents a group of formula -R⁵, in which R⁵ is as defined in Claim 1;

R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;

R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;

X represents an oxygen atom; and

45 A represents a 1,4-piperazin-1,4-diyl group.

24. A compound according to Claim 1, in which:

at least one of R¹ and R² represents an aryl group which is substituted by at least one of substituents (a), defined in Claim 1;

R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;

50 R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;

X represents an oxygen atom; and

A represents a 1,4-piperazin-1,4-diyl group.

25. A compound according to Claim 1, in which:

55 R¹ represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl, C₁ - C₂₂ alkoxy or halogen substituent;

R² represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or C₁ - C₆ haloalkyl and/or halogen substituent;

R³ represents a hydrogen atom;

R⁴ represents a substituted phenyl group having from 1 to 3 C₁ - C₆ alkoxy substituents;

B represents a carbonyl group;

X represents an oxygen atom; and

5 A represents a 1,4-piperazin-1,4-diyl group.

26. 1-[3-(3,4-Dimethoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

27. 1-[3,3-Bis(3-chlorophenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

28. 1-[3,3-Bis(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

29. 1-[3,3-Bis(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

10 30. 1-[3-(2-Chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

31. 1-[3-(2-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

32. 1-[3-(2-Chlorophenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

33. 1-[3-(3-Chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

34. 1-[3-(3-Chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

15 35. 1-[3-(3-Chlorophenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

36. 1-[3-(3-Chlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

37. 1-[3-(3-Chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

38. 1-[3-(3-Chlorophenyl)-3-(4-methoxy-3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine.

20 39. 1-[3-(3-Chlorophenyl)-3-(3,4-dipropoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

40. 1-[3-(3,4-Dichlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

41. 1-[3-(3,4-Dichlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

42. 1-[3-(3-Trifluoromethylphenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

43. 1-[3-(3-Trifluoromethylphenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

25 44. 1-[3-(3-Trifluoromethylphenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine.

45. 1-[3-(3-Methylphenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

46. 1-[3-(3-Methylphenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

47. 1-[3-(3-Methoxy-4-propoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

30 48. 1-[3-(3,4-Dipropoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

49. 1-[3-(4-Ethoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

50. 1-[3-(4-Butoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

51. 1-[3-(3-Methoxy-4-propoxyphenyl)-3-(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine.

35 52. 1-[3-(3-Methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)-piperazine.

53. 1-[3-(3-Chlorophenyl)-3-(3-methoxy-4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

54. 1-[3-(3-Chlorophenyl)-3-(4-ethoxy-3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.

40 55. A pharmaceutical composition for the treatment or prophylaxis of PAF-related diseases and disorders, comprising a PAF antagonist in combination with a pharmaceutically acceptable carrier or diluent, in which the PAF antagonist is at least one compound according to any one of Claims 1 to 54.

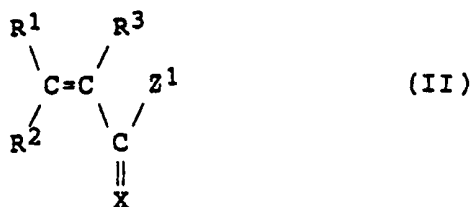
56. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 54, in medicine.

45 57. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 54, for the treatment or prophylaxis of a PAF-mediated pathology.

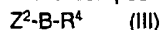
58. The use according to Claim 57, in which said pathology is psoriasis, nephritis, asthma, inflammation or shock.

59. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of Claims 1 to 54, for the manufacture of medicament for the treatment or prophylaxis of a PAF-mediated pathology, such as psoriasis, nephritis, asthma, inflammation or shock.

50 60. A process for preparing a compound according to any one of Claims 1 to 54, which process comprises reacting a compound of formula (II):



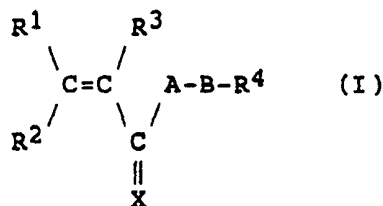
with a compound of formula (III):



[in which one of Z^1 , in formula (II), and Z^2 , in formula (III), represents a group represented by Y and the other of Z^1 and Z^2 represents a group of formula -A-H ; Y represents a nucleophilic leaving group; and R^1 , R^2 , R^3 , R^4 , X, A and B are as defined in Claim 1).

Claims for the following Contracting States: ES; GR

1. A process for preparing a compound of formula (I):



[in which:

R^1 and R^2 are the same or different, and each represents a group having the formula -R^5 , -CH=CH-R^5 or -C=C-R^5 ,

in which R^5 represents a C_6 - C_{14} carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a), defined below, or an aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (a), defined below;

R^3 represents a hydrogen atom, a C_1 - C_6 alkyl group, a cyano group, or a group having the formula -R^5 , in which R^5 is as defined above;

X represents an oxygen atom or a sulphur atom;

A represents a 1,4-piperazin-1,4-diyl group or a 1,4-homopiperazin-1,4-diyl group;

B represents a C_1 - C_6 alkylene group, a carbonyl group, a thiocarbonyl group, a sulphonyl group or a sulphonyl group;

R^4 represents an unsubstituted phenyl group or a substituted phenyl group having from 1 to 5 of substituents (a) and/or substituents (b), defined below;

substituents (a):

C_1 - C_{22} alkyl groups; C_1 - C_{22} alkoxy groups; C_1 - C_6 haloalkyl groups; hydroxy groups; C_1 - C_1 alkylenedioxy groups; C_1 - C_{22} aliphatic carboxylic acyloxy groups; substituted C_1 - C_6 aliphatic carboxylic acyloxy groups which are substituted by at least one of substituents (c), defined below; C_7 - C_{15} carbocyclic aromatic carboxylic acyloxy groups; substituted C_7 - C_{15} carbocyclic aromatic carboxylic acyloxy groups which are substituted by at least one of substituents (d), defined below; C_8 - C_{11} aralkyloxycarbonyloxy groups in which the aryl part is unsubstituted or is substituted by at least one of substituents (d), defined below; C_1 - C_6 alkanesulphonyloxy groups in which the alkane part is unsubstituted or is substituted by at least one of substituents (c), defined below; arylsulphonyloxy groups in which the aryl part is unsubstituted or is substituted by at least one of substituents (d), defined below; halogen atoms, and nitro groups;

substituents (b):

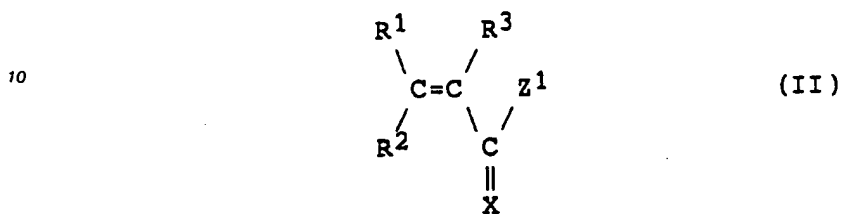
C_1 - C_6 alkylsulphonyl groups; C_1 - C_6 alkylsulphonyl groups; and C_1 - C_6 alkylthio groups;

substituents (c):

C₁ - C₆ alkyl groups; C₁ - C₆ haloalkyl groups; halogen atoms; C₁ - C₆ alkoxy groups; and (C₁ - C₆ alkanoyloxy)methoxycarbonyl groups;

substituents (d):

- 5 C₁ - C₆ alkyl groups; C₁ - C₆ alkoxy groups; halogen atoms; unsubstituted C₆ - C₁₀ aryl groups; nitro groups; and (C₁ - C₆ alkoxy)carbonyl groups;]
or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



with a compound of formula (III):

Z²-B-R⁴ (III)

- 20 [in which one of Z¹, in formula (II), and Z², in formula (III), represents a group represented by Y and the other of Z¹ and Z² represents a group of formula -A-H; Y represents a nucleophilic leaving group; and R¹, R², R³, R⁴, X, A and B are as defined above).

2. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which:

- 25 R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵, in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a'), defined below, or an aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said heterocyclic group being unsubstituted or being substituted by at least one of substituents (a'), defined below;
R⁴ represents an unsubstituted phenyl group or a substituted phenyl group having from 1 to 5 of
30 substituents (a'), defined below, and/or substituents (b), defined in Claim 1;

substituents (a'):

C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; hydroxy groups; C₁ - C₄ alkylenedioxy groups; halogen atoms; and nitro groups.

- 35 3. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which:

R¹ and R² are the same or different, and each represents a group having the formula -R⁵, -CH=CH-R⁵ or -C≡C-R⁵,

- 40 in which R⁵ represents a C₆ - C₁₄ carbocyclic aryl group which is unsubstituted or is substituted by at least one of substituents (a''), defined below, or an unsubstituted aromatic heterocyclic group having from 5 to 14 ring atoms, of which from 1 to 5 are nitrogen and/or sulphur hetero-atoms; R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;

A represents a 1,4-piperazin-1,4-diyl group;

B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;

- 45 R⁴ represents a substituted phenyl group having from 1 to 5 of substituents (a''), defined below; and
substituents (a''):

C₁ - C₂₂ alkyl groups; C₁ - C₂₂ alkoxy groups; C₁ - C₆ haloalkyl groups; C₁ - C₄ alkylenedioxy groups; and halogen atoms.

4. A process according to Claim 3, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which:

- 50 at least one of R¹ and R² represents an aryl group which is substituted by at least one of substituents (a''), defined in Claim 3;

R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

X represents an oxygen atom;

A represents a 1,4-piperazin-1,4-diyl group; and

- 55 B represents a carbonyl group.

5. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R¹ and R² are the same or different and each represents a group of formula -R⁵, in which R⁵ is as defined in Claim 1.

6. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R¹ and R² each represents a group R⁵, and R⁵ represents an aryl group.

7. A process according to Claim 6, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which one of the groups represented by R⁵ is a substituted phenyl group and the other is an unsubstituted phenyl group or a substituted phenyl group.

8. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R¹ represents a substituted phenyl group having at least one of said alkyl, alkoxy or halogen substituents and R² represents an unsubstituted phenyl group or a substituted phenyl group having at least one of said alkyl, haloalkyl and halogen substituents.

9. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R¹ represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl, C₁ - C₂₂ alkoxy or halogen substituent.

10. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R¹ represents a substituted phenyl group having at least one C₁ - C₆ alkyl, C₁ - C₆ alkoxy or halogen substituent.

11. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R² represents an unsubstituted phenyl group or a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or C₁ - C₆ haloalkyl and/or halogen substituent.

12. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R² represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₆ haloalkyl and/or halogen substituent.

13. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R² represents a substituted phenyl group having at least one C₁ - C₆ alkyl and/or C₁ - C₆ haloalkyl and/or halogen substituent.

14. A process according to any one of Claims 11 to 13, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which the substituent on R² is at the meta position.

15. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R³ represents a hydrogen atom or a C₁ - C₆ alkyl group.

16. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R³ represents a hydrogen atom.

17. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which X represents an oxygen atom.

18. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which B represents a carbonyl group.

19. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents.

20. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R⁴ represents a phenyl group having at least one C₁ - C₃ alkoxy substituent.

21. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which R⁴ represents a 3,4-dimethoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl or 3,4,5-trimethoxyphenyl group.

22. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which A represents a 1,4-piperazin-1,4-diyl group.

23. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which:

R¹ and R² are the same or different and each represents a group of formula -R⁵, in which R⁵ is as defined in Claim 1;

R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;

R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;

B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;

X represents an oxygen atom; and

A represents a 1,4-piperazin-1,4-diyl group.

24. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which:
at least one of R¹ and R² represents an aryl group which is substituted by at least one of substituents (a), defined in Claim 1;
- 5 R³ represents a hydrogen atom or a C₁ - C₆ alkyl group;
R⁴ represents a substituted phenyl group having from 1 to 5 C₁ - C₆ alkoxy substituents;
B represents a C₁ - C₆ alkylene group, a carbonyl group, a thiocarbonyl group or a sulphonyl group;
X represents an oxygen atom; and
A represents a 1,4-piperazin-1,4-diyl group.
- 10 25. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare a compound of formula (I) or a salt thereof, in which:
R¹ represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl, C₁ - C₂₂ alkoxy or halogen substituent;
R² represents a substituted phenyl group having at least one C₁ - C₂₂ alkyl and/or C₁ - C₂₂ alkoxy and/or
15 C₁ - C₆ haloalkyl and/or halogen substituent;
R³ represents a hydrogen atom;
R⁴ represents a substituted phenyl group having from 1 to 3 C₁ - C₆ alkoxy substituents;
B represents a carbonyl group;
X represents an oxygen atom; and
20 A represents a 1,4-piperazin-1,4-diyl group.
26. A process according to Claim 1, in which the reagents and reaction conditions are so chosen as to prepare:
1-[3-(3,4-dimethoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-bis(3-chlorophenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
25 1-[3-bis(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-bis(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(2-chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(2-chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(2-chlorophenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
30 1-[3-(3-chlorophenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-chlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-chlorophenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-chlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
35 1-[3-(3-chlorophenyl)-3-(4-methoxy-3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-chlorophenyl)-3-(3,4-dipropoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3,4-dichlorophenyl)-3-(4-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3,4-dichlorophenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-trifluoromethylphenyl)-3-(3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
40 1-[3-(3-trifluoromethylphenyl)-3-(3-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-trifluoromethylphenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-methylphenyl)-3-(3,4-dimethoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-methylphenyl)-3-(4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-methoxy-4-propoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
45 1-[3-(3,4-dipropoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(4-ethoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(4-butoxy-3-methoxyphenyl)-3-phenylacryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-methoxy-4-propoxyphenyl)-3-(3-trifluoromethylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
1-[3-(3-methoxy-4-propoxyphenyl)-3-(3-methylphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine;
50 1-[3-(3-chlorophenyl)-3-(3-methoxy-4-propoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine; or
1-[3-(3-chlorophenyl)-3-(4-ethoxy-3-methoxyphenyl)acryloyl]-4-(3,4,5-trimethoxybenzoyl)piperazine.
27. A process for preparing a pharmaceutical composition for the treatment or prophylaxis of PAF-related diseases and disorders, by mixing a PAF antagonist with a pharmaceutically acceptable carrier or diluent, in which the PAF antagonist is at least one compound according to any one of Claims 1 to 26.
- 55 28. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 26, for the treatment or prophylaxis of a PAF-mediated pathology.
29. The use according to Claim 28, in which said pathology is psoriasis, nephritis, asthma, inflammation or shock.

30. The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined in any one of Claims 1 to 26, for the manufacture of medicament for the treatment or prophylaxis of a PAF-mediated pathology, such as psoriasis, nephritis, asthma, inflammation or shock.

5

10

15

20

25

30

35

40

45

50

55